L10 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:76588 CAPLUS
TITLE: Combinations comprising epothilones and antiproliferative uses thereof
INVENTOR(S): Chen, Tianling; Greeley, Diane; Rothermel, John David; Wartmann, Markus; Wood, Jeanette Marjorie
PATENT ASSIGNEE(S): Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007924	A2	20030130	WO 2002-EP8020	20020718

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR

PRIORITY APPLN. INFO.: US 2001-306559P P 20010719
US 2001-306560P P 20010719
US 2001-306571P P 20010719

AB The invention relates to a combination which comprises (a) a **bisphosphonate**, a platinum compd. or a vasculostatic compd. and (b) an epothilone deriv. of formula (I), wherein A represents O or NRN, wherein RN is hydrogen or lower alkyl, R is hydrogen or lower alkyl, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier for simultaneous, sep. or sequential use, in particular for the delay of progression or treatment of a proliferative disease, esp. a solid **tumor** disease; a pharmaceutical compn., a com. package or product comprising such a combination; the use of such a combination for the prepn. of a medicament for the delay of progression or treatment of a proliferative disease and to a method of treatment of a warm-blooded animal.

IT INDEXING IN PROGRESS
IT Animal cell line
(DU-145; combinations comprising epothilones and antiproliferative uses thereof)
IT Animal cell line
(PC-3MM2; combinations comprising epothilones and antiproliferative uses thereof)
IT Drug delivery systems
(carriers; combinations comprising epothilones and antiproliferative uses thereof)
IT Uterus, **neoplasm**
(cervix; combinations comprising epothilones and antiproliferative uses thereof)
IT Intestine, **neoplasm**
(colon; combinations comprising epothilones and antiproliferative uses thereof)
IT **Angiogenesis** inhibitors
Antitumor agents
Cytotoxic agents

Drug delivery systems
Human
Lung, **neoplasm**
Ovary, **neoplasm**
(combinations comprising epothilones and antiproliferative uses thereof)

IT Bone, **neoplasm**
(metastasis, of prostate **cancer**; combinations comprising epothilones and antiproliferative uses thereof)

IT Prostate gland
(**neoplasm**, hormone-refractory; combinations comprising epothilones and antiproliferative uses thereof)

IT Head
Neck, anatomical
(**neoplasm**; combinations comprising epothilones and antiproliferative uses thereof)

IT Disease, animal
(proliferative; combinations comprising epothilones and antiproliferative uses thereof)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**bisphosphonate**; combinations comprising epothilones and antiproliferative uses thereof)

IT **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid **40391-99-9**, Pamidronic acid 41575-94-4, Carboplatin 61825-94-3, Oxaliplatin **66376-36-1**, Alendronic acid **89987-06-4**, Tiludronic acid **105462-24-6**, Risedronic acid **114084-78-5**, Ibandronic acid **118072-93-8**, **Zoledronic** acid 152044-54-7D, Epothilone b, derivs. 212142-18-2, ptk787
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(combinations comprising epothilones and antiproliferative uses thereof)

L10 ANSWER 2 OF 25. CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:44926 CAPLUS
DOCUMENT NUMBER: 138:100267
TITLE: The use of **zoledronic** acid, a novel, highly potent **bisphosphonate**, for the treatment of hypercalcemia of malignancy
AUTHOR(S): Major, Pierre
CORPORATE SOURCE: Department of Medicine, McMaster University, Hamilton, ON, Can.
SOURCE: Oncologist (2002), 7(6), 481-491
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Hypercalcemia of malignancy is a serious complication of **cancer** that affects patients with and without bone metastases. A single infusion of pamidronate disodium, a nitrogen-contg. **bisphosphonate**, effectively normalizes serum calcium in the majority of patients treated for up to 1 mo. **Zoledronic** acid is a new-generation, heterocyclic nitrogen-contg. **bisphosphonate** and the most potent inhibitor of bone resorption identified to date. The natural history, clin. presentation, and treatment of hypercalcemia of malignancy are reviewed, with a focus on the mechanisms of action and relative efficacy and safety of **bisphosphonate** therapies. The

improved efficacy of **zoledronic** acid compared with pamidronate disodium has been demonstrated in a pooled anal. of two randomized clin. trials in patients with hypercalcemia of malignancy. In these trials, both **zoledronic** acid and pamidronate disodium were safe and well tolerated; however, **zoledronic** acid treatment resulted in a significantly higher no. of complete responses, more rapid calcium normalization, and more durable responses compared with pamidronate disodium. Given the superior efficacy and comparable safety profile of **zoledronic** acid compared with pamidronate disodium, **zoledronic** acid is likely to become the treatment of choice for hypercalcemia of malignancy.

IT Bone, **neoplasm**
(metastasis; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT Bone
(resorption, inhibitors; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT Human
Neoplasm
(use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:948341 CAPLUS
TITLE: Pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma
AUTHOR(S): Gordon, Sharon; Helfrich, Miep H.; Sati, Hamdi I. A.; Greaves, Michael; Ralston, Stuart H.; Culligan, Dominic J.; Soutar, Richard L.; Rogers, Michael J.
CORPORATE SOURCE: Department of Medicine and Therapeutics, University of Aberdeen Medical School, Aberdeen, UK
SOURCE: British Journal of Haematology (2002), 119(2), 475-483
CODEN: BJHEAL; ISSN: 0007-1048
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Anti-resorptive **bisphosphonates**, such as pamidronate, are an effective treatment for osteolytic disease and hypercalcemia in patients with multiple myeloma, but have also been shown to cause apoptosis of myeloma cell lines in vitro. In this study, we found that a single infusion of pamidronate, in 16 newly diagnosed patients with multiple myeloma, caused a marked increase in apoptosis of plasma cells in vivo in 10 patients and a minimal increase in four patients ($P < 0.05$). The nitrogen-contg. **bisphosphonates** pamidronate and

zoledronic acid also induced apoptosis of authentic, human bone marrow-derived plasma cells in vitro. Apoptosis of plasma cells in vitro was probably caused by inhibition of the mevalonate pathway and loss of prenylated small GTPases, as even low concns. (.gtoreq. 1 .mu.mol/l) of **zoledronic** acid caused accumulation of unprenylated Rap1A in cultures of bone marrow mononuclear cells in vitro. GGTI-298, a specific inhibitor of geranylgeranyl transferase I, also induced apoptosis in human plasma cells in vitro, suggesting that geranylgeranylated proteins play a role in signaling pathways that prevent plasma cell death. Our results suggest that pamidronate may have direct and/or indirect anti-**tumor** effects in patients with multiple myeloma, which has important implications for the further development of the more potent nitrogen-contg. **bisphosphonates**, such as **zoledronic** acid, in the treatment of myeloma.

IT Multiple myeloma
(inhibitor; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Antitumor agents
(multiple myeloma; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Apoptosis
Human
Prenylation
Signal transduction, biological
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Lymphocyte
(plasma cell; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Bone marrow
(plasma cells; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Alkenylation
(tetramethylhexadecatetraenylation; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT 9059-32-9 135371-29-8, Geranylgeranyl transferase I 180977-44-0, GGTI-298
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT **40391-99-9** 57248-88-1, Aredia **118072-93-8**, Zometa
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:888561 CAPLUS
DOCUMENT NUMBER: 137:363054
TITLE: Combination comprising N-{5-[4-(4-methylpiperazinomethyl)benzoylamino]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidineamine and a chemotherapeutic agent
INVENTOR(S): Bruns, Christian; Buchdunger, Elisabeth; O'Reilly, Terence; Silberman, Sandra Leta; Wartmann, Markus;

Weckbecker, Gisbert
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092091	A1	20021121	WO 2002-EP5362	20020515

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2001-291427P P 20010516

AB A method of treating a warm-blooded animal, esp. a human, having a proliferative disease or acute or chronic transplant rejection comprises administering to the animal a combination contg. comprises (a) N-{5-[4-(4-methylpiperazinomethyl)benzoylamino]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidineamine (imatinib) and (b) a chemotherapeutic agent selected from antineoplastic agents, esp. as defined herein, and agents effective in treating acute or chronic transplant rejection; a combination comprising (a) and (b) as defined above and optionally at least 1 carrier for simultaneous, sep. or sequential use, in particular for the delay of progression or treatment of a proliferative disease, esp. a solid **tumor** disease. That STI 571 (mesylate of imatinib) induces synergistic therapeutic interactions with Taxol in rat glioma **tumor** xenografts in female mice.

IT Androgens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiandrogens; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Estrogens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiestrogens; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Prostate gland
(carcinoma; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Alkylating agents, biological
Antitumor agents
Human
Microtubule
(combination comprising imatinib and chemotherapeutic antitumor agent)

IT Bone, **neoplasm**
(metastasis; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Drug interactions
(synergistic; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Transplant and Transplantation
(treatment of rejection of; combination comprising imatinib and chemotherapeutic antitumor agent)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; combination comprising imatinib and chemotherapeutic antitumor agent)
IT 33515-09-2, Gonadorelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination comprising imatinib and chemotherapeutic antitumor agent)
IT 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 112809-51-5, Letrozole 114977-28-5, Docetaxel **118072-93-8, Zoledronic** acid 152459-95-5, Imatinib 180288-69-1, Trastuzumab 220127-57-1, STI 571
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination comprising imatinib and chemotherapeutic antitumor agent)
IT 9039-48-9, Aromatase 142805-56-9, Topoisomerase II 143180-75-0 372092-80-3, Protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination comprising imatinib and chemotherapeutic antitumor agent)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:884654 CAPLUS
DOCUMENT NUMBER: 137:362484
TITLE: Pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases
AUTHOR(S): Chen, Tianling; Berenson, James; Vescio, Robert; Swift, Regina; Gilchick, Alicia; Goodin, Susan; LoRusso, Patricia; Ma, Peiming; Ravera, Christina; Deckert, Fabienne; Schran, Horst; Seaman, John; Skerjanec, Andrej
CORPORATE SOURCE: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
SOURCE: Journal of Clinical Pharmacology (2002), 42(11), 1228-1236
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics, pharmacodynamics, and safety of **zoledronic** acid (Zometa), a new-generation **bisphosphonate**, were evaluated in 36 patients with **cancer** and bone metastases. **Zoledronic** acid (by specific RIA) and markers of bone turnover were detd. in plasma and urine after three consecutive infusions (qx28 days) of 4 mg/5 min (n = 5), 4 mg/15 min (n = 7), 8 mg/15 min (n = 12), or 16 mg/15 min (n = 12). **Zoledronic** plasma disposition was multiphasic, with half-lives of 0.2 and 1.4 h representing an early, rapid decline of concns. from the end-of-infusion Cmax to < 1% of Cmax at 24 h postdose and half-lives of 39 and 4526 h describing subsequent phases of very low concns. between days 2 and 28 postdose. AUC0-24 h and Cmax were dose proportional and showed little accumulation (AUC0.24 h ratio between the third and first dose was 1.28). Prolonging the infusion from 5 to 15 min lowered Cmax by 34%, with no effect on AUC0-24 h. Urinary excretion of **zoledronic** acid was independent of in fusion duration, dose, or no. of doses, showing av. Ae0-24 h of 38% .+-. 13%, 41% .+-. 14%, and 37% .+-. 17%, resp., after 4, 8, and 16 mg. Only trace amts. of drug were detectable in post 24-h urines. Renal clearance (Ae0-24 h)/(AUC0-24 h) was on av. 69.+-.28, 81.+-.40, and 54.+-.34 mL/min after 4, 8, and 16 mg, resp., and showed a moderate correlation (r = 0.5; p < 0.001) with creatinine clearance, which was 84.+-.23, 82.+-.25, and 80.+-.40 mL/min

for the dose groups at baseline. Adverse events and changes from baseline in vital signs and clin. lab. variables showed no relationship in terms of type, frequency, or severity with **zoledronic** acid dose or pharmacokinetic parameters. **Zoledronic** acid produced significant declines from baseline in serum and/or creatinine-cor. urine C-telopeptide (by 74%), N-telopeptide (69%), pyridinium cross-links (19-33%), and calcium (62%), with an increasing trend (by 12%) in bone alk. phosphatase. There was no relationship of the magnitude and duration of these changes with **zoledronic** acid dose, Ae0-24 h, AUC0-24 h, or Cmax. The antiresorptive effects were evident within 1 day postdose and were maintained over 28 days across all dose levels, supporting monthly dosing with 4 mg **zoledronic** acid.

IT Bone, **neoplasm**
(metastasis; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Human
Neoplasm
(pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Bone
(resorption, inhibitors; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Bone
(resorption; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT **118072-93-8**, Zometa
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:866298 CAPLUS
DOCUMENT NUMBER: 137:320061
TITLE: **Zoledronic** acid reduces skeletal-related events in patients with osteolytic metastases: A double-blind, randomized dose-response study. [Erratum to document cited in CA135:189951]
AUTHOR(S): Berenson, James R.; Rosen, Lee S.; Howell, Anthony; Porter, Lester; Coleman, Robert E.; Morley, Walter; Dreicer, Robert; Kuross, Steven A.; Lipton, Allan; Seaman, John J.
CORPORATE SOURCE: Cedars-Sinai Medical Center, Los Angeles, CA, USA
SOURCE: Cancer (New York, NY, United States) (2001), 91(10), 1956
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cor. address for reprints is: James R. Berenson, M.D., Cedars-Sinai Medical Center, Bev. Mod. 1, Room 100, 8700 Beverly Boulevard, Los

Angeles, CA 90048; Fax: (310)423-1977; E-mail: berensonj@cshs.org.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

IT Human
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

IT **118072-93-8, Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

L10 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:849414 CAPLUS
DOCUMENT NUMBER: 137:346153
TITLE: Pharmaceutical uses of **bisphosphonates**
INVENTOR(S): Seaman, John J.
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087555	A2	20021107	WO 2002-EP4771	20020430

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2001-288220P P 20010502
OTHER SOURCE(S): MARPAT 137:346153

AB A method for the treatment of prostate **cancers** and other **cancers** having assocd. osteoblastic (osteosclerotic) metastases in a patient in need of such treatment comprising administering an effective amt. of an N-**bisphosphonate**, esp. **zoledronic** acid or a salt or any hydrate thereof, to the patient. **Bisphosphonates** are formulated into various delivery systems, such as capsules, adhesive transdermal system, and injections. For example, **zoledronic** acid 4 mg, given as a 15-min infusion, was well tolerated. **Zoledronic** acid 4 mg 15-min infusions every 3 wk significantly reduce skeletal-related events in patients with metastatic prostate **cancer** refractory to hormonal therapy.

IT Antitumor agents
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Human
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases in humans)

IT Drug delivery systems
(capsules; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Drug delivery systems

(injections; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Bone, **neoplasm**
(metastasis; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Prostate gland
(**neoplasm**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Drug delivery systems
(transdermal; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 197313-76-1, **NE 10244**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10244**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 183490-29-1, **NE 10446**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10446**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 132508-02-2, U 81581
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(U 81581; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **40391-99-9**, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8** **66376-36-1**, Alendronic acid **79778-41-9**, 6-Amino-1-hydroxyhexane-1,1-diphosphonic acid **105462-24-6**, Risedronic acid 112855-84-2, FR 78844 **114084-78-5**, Ibandronic acid **118072-93-8**, **Zoledronic** acid **125946-92-1**, EB 1053 131654-46-1 132423-94-0 **180064-38-4**, YM 529
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

L10 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:842416 CAPLUS
DOCUMENT NUMBER: 137:320059
TITLE: A randomized, placebo-controlled trial of **zoledronic** acid in patients with hormone-refractory metastatic prostate carcinoma
AUTHOR(S): Saad, Fred; Gleason, Donald M.; Murray, Robin; Tchekmedyian, Simon; Venner, Peter; Lacombe, Louis; Chin, Joseph L.; Vinholes, Jeferson J.; Goas, J. Allen; Chen, Bee
CORPORATE SOURCE: Zoledronic Acid Prostate Cancer Study Group, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Can.
SOURCE: Journal of the National Cancer Institute (2002), 94(19), 1458-1468
CODEN: JNCIEQ; ISSN: 0027-8874
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone metastases are a common cause of morbidity in patients with prostate carcinoma. We studied the effect of a new **bisphosphonate**, **zoledronic** acid, which blocks bone destruction, on skeletal

complications in prostate **cancer** patients with bone metastases. Patients with hormone-refractory prostate **cancer** and a history of bone metastases were randomly assigned to a double-blind treatment regimen of i.v. **zoledronic** acid at 4 mg (N = 214), **zoledronic** acid at 8 mg (subsequently reduced to 4 mg; 8/4) (N = 221), or placebo (N = 208) every 3 wk for 15 mo. Proportions of patients with skeletal-related events, time to the first skeletal-related event, skeletal morbidity rate, pain and analgesic scores, disease progression, and safety were assessed. All statistical tests were two-sided. Approx. 38% of patients who received **zoledronic** acid at 4 mg, 28% who received **zoledronic** acid at 8/4 mg, and 31 % who received placebo completed the study. A greater proportion of patients who received placebo had skeletal-related events than those who received **zoledronic** acid at 4 mg (44.2 % vs. 33.2 %; difference = -11.0 %, 95% confidence interval [CI] = -20.3% to -1.8%; P = .021) or those who received **zoledronic** acid at 8/4 mg (38.5%; difference vs. placebo = -5.8%, 95% CI = -15.1% to 3.6%; P = .222). Median time to first skeletal-related event was 321 days for patients who received placebo, was not reached for patients who received **zoledronic** acid at 4 mg (P = .011 vs. placebo), and was 363 days for those who received **zoledronic** acid at 8/4 mg (P = .491 vs. placebo). Compared with urinary markers in patients who received placebo, urinary markers of bone resorption were statistically significantly decreased in patients who received **zoledronic** acid at either dose (P = .001). Pain and analgesic scores increased more in patients who received placebo than in patients who received **zoledronic** acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups. **Zoledronic** acid at 4 mg given as a 15-min infusion was well tolerated, but the 8-mg dose was assocd. with renal function deterioration. **Zoledronic** acid at 4 mg reduced skeletal-related events in prostate **cancer** patients with bone metastases.

IT Prostate gland
(carcinoma, metastasis; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT Bone, **neoplasm**
(metastasis; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT Antitumor agents
Human
(new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT **118072-93-8**, Zometa
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:793432 CAPLUS
DOCUMENT NUMBER: 137:304812
TITLE: A drug for use in bone grafting
INVENTOR(S): Little, David Graham

PATENT ASSIGNEE(S): The Royal Alexandra Hospital for Children, Australia
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080933	A1	20021017	WO 2002-AU412	20020328

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
AU 2001-4187 A 20010403
AU 2001-9613 A 20011217

AB A drug and method for bone grafting which improves the osteoinductive and/or osteoconductive potential of a bone graft, bone graft substitute or extenders. The drug is selected from the group consisting of **bisphosphonates** which may be administered to a subject either prior to, during or after a bone grafting procedure.

IT Bone morphogenetic proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(7; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-2; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-4; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-6; drug for use in bone grafting)
IT Transplant and Transplantation
(allotransplant; drug for use in bone grafting)
IT Spinal column
(arthrodesis; drug for use in bone grafting)
IT Joint, anatomical
(arthroplasty; drug for use in bone grafting)
IT Bone
(artificial; drug for use in bone grafting)
IT Infection
(bone loss due to; drug for use in bone grafting)
IT Transplant and Transplantation
(bone, substitutes or extenders; drug for use in bone grafting)
IT Transplant and Transplantation
(bone; drug for use in bone grafting)
IT Drug delivery systems
(carriers; drug for use in bone grafting)
IT Osteoarthritis
(congenital pseudo-; drug for use in bone grafting)
IT Bone, disease
(delayed union or non-union of a bone; drug for use in bone grafting)
IT Bone
(demineralization; drug for use in bone grafting)
IT Metabolism, animal

(disorder; drug for use in bone grafting)
IT Bone marrow
Cement
Cyst, pathological
Human
Human
Hyperparathyroidism
Neoplasm
Osteomyelitis
Putty
Skull
Sponges (artificial)
Surgery
(drug for use in bone grafting)
IT Collagens, biological studies
Gelatins, biological studies
Osteocalcins
Polymers, biological studies
Resins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
IT Kidney, disease
(failure; drug for use in bone grafting)
IT Bone, disease
(fracture, open; drug for use in bone grafting)
IT Bone, disease
(fracture; drug for use in bone grafting)
IT Drug delivery systems
(gels; drug for use in bone grafting)
IT Drug delivery systems
(implants; drug for use in bone grafting)
IT Drug delivery systems
(injections, i.m.; drug for use in bone grafting)
IT Drug delivery systems
(injections, i.v.; drug for use in bone grafting)
IT Jaw
(mandibula; drug for use in bone grafting)
IT Jaw
(maxilla; drug for use in bone grafting)
IT Medical goods
(meshes; drug for use in bone grafting)
IT Bone
(minerals; drug for use in bone grafting)
IT Drug delivery systems
(oral; drug for use in bone grafting)
IT Surgery
(orthopedic; drug for use in bone grafting)
IT Bone, disease
(osteolysis; drug for use in bone grafting)
IT Drug delivery systems
(parenterals; drug for use in bone grafting)
IT Drug delivery systems
(s.c.; drug for use in bone grafting)
IT Medical goods
(sheets, flexible; drug for use in bone grafting)
IT Drug delivery systems
(solns., injection; drug for use in bone grafting)
IT Bone
(tibia; drug for use in bone grafting)
IT Drug delivery systems
(transdermal; drug for use in bone grafting)
IT Bone

(transplant, substitutes or extenders; drug for use in bone grafting)
IT Bone
(transplant; drug for use in bone grafting)
IT Injury
(trauma; drug for use in bone grafting)
IT Transplant and Transplantation
(xenotransplant; drug for use in bone grafting)
IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-; drug for use in bone grafting)
IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; drug for use in bone grafting)
IT **2809-21-4 10596-23-3 40391-99-9**
66376-36-1, Alendronate **79778-41-9**, Neridronate
89987-06-4, Tiludronate **105462-24-6 114084-78-5**
, Ibandronate **118072-93-8**, **Zoledronic** acid
121368-58-9, Olpadronate **125946-92-1**, EB-1053 138330-18-4,
Incadronate **180064-38-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
IT 56-81-5, Glycerol, biological studies 7440-70-2D, Calcium, compds.
7778-18-9, Osteoset 26009-03-0, Polyglycolic acid 26023-30-3,
Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid
26124-68-5, Polyglycolic acid 61912-98-9, Insulinlike growth factor
62031-54-3, Fibroblast growth factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:780471 CAPLUS
DOCUMENT NUMBER: 137:288664
TITLE: **Zoledronic** acid is effective in the treatment of prostate **cancer** patients with bone metastases
AUTHOR(S): Maung, Kavita; Higano, Celestia
CORPORATE SOURCE: USA
SOURCE: Clinical Prostate Cancer (2002), 1(1), 12-13
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study included adult patients with prostate **cancer** and bone metastases, an Eastern Cooperative Oncol. Group performance status (PS) of .ltoreq.2, and serum creatinine levels of .ltoreq.3 mg/dL. Patients were required to have rising prostate-specific antigen levels and base-line serum testosterone < 50 mg/dL. Patients were randomized to treatment with either **zoledronic** acid 4 mg or 8 mg or placebo to be given 5-min infusion every 3 wk. There was a statistically significant redn. in SREs (skeletal-related events) seen in the **zoledronic** acid arm. Thirty-three percent of patients on the **zoledronic** acid arm experienced SREs - compared to 44% of patients on the placebo arm (P = 0.021). Patients receiving 4 mg of **zoledronic** acid showed significantly reduced frequency of SREs and increased time to first SRE compared to patients on placebo. The overall median survival was not significantly increased in patients treated with **zoledronic** acid compared to placebo. Based on these promising results, the US FDA has recently approved **zoledronic** acid for the treatment of bone

metastases in patients who have failed initial hormonal therapy for prostate **cancer**.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Prostate gland
(**neoplasm**, metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Antitumor agents
(prostate **cancer** bone metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Human
(**zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:651461 CAPLUS
DOCUMENT NUMBER: 137:194877
TITLE: Novel approaches to the management of bone metastases in patients with breast **cancer**
AUTHOR(S): Hortobagyi, Gabriel N.
CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Seminars in Oncology (2002), 29(3, Suppl. 11), 134-144
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Bone metastases appear frequently in patients with advanced breast **cancer**. They are assocd. with substantial morbidity and occasionally produce life-threatening complications. Systemic anticancer therapies (chemotherapy and hormonal therapies) represent the treatment of choice for these and other distant metastases from breast **cancer**. Aggressive use of prophylactic and therapeutic orthopedic surgery is warranted, esp. for lesions in wt.-bearing areas. Judicious use of external radiotherapy and bone-seeking radionuclides contributes to the control of pain and local control of lesions in strategic locations. In recent years, the development of osteoclast-inhibitory therapy added a new dimension to symptom control and prevention of skeletal complications. The **bisphosphonates**, clodronate, pamidronate, and **zoledronic** acid, are potent osteoclast inhibitors with marked clin. effects. They represent the drugs of choice for control of hypercalcemia of malignancy, and they are crit. adjuvants to systemic anticancer therapy of metastatic disease. More recently, the development of recombinant osteoprotegerin and an anti-parathyroid hormone-related protein monoclonal antibody represent promising new options for the treatment of patients with bone metastases.

IT Antitumor agents
(breast **cancer** bone metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Bone, **neoplasm**
(metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Mammary gland
(**neoplasm**, metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Human
Radiotherapy
(novel approaches to management of bone metastases in patients with breast **cancer**)
IT Surgery
(orthopedic; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Bone
(resorption inhibitor; novel approaches to management of bone metastases in patients with breast **cancer**)
IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; novel approaches to management of bone metastases in patients with breast **cancer**)
IT **10596-23-3 40391-99-9 118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel approaches to management of bone metastases in patients with breast **cancer**)
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:539062 CAPLUS
DOCUMENT NUMBER: 137:226194
TITLE: Highly Potent Geminal **Bisphosphonates**. From Pamidronate Disodium (Aredia) to **Zoledronic** Acid (Zometa)
AUTHOR(S): Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber, Gerard; Seltenmeyer, Yves; Green, Jonathan R.
CORPORATE SOURCE: Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** (BPs) are pyrophosphate analogs in which the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was the starting point for extensive SAR studies. Small changes of the structure of pamidronate lead to marked improvements of the inhibition of osteoclastic resorption potency. Alendronate (1c, MSD), with an extra methylene group in the N-alkyl chain, and olpadronate

(1h, Gador), the N,N-di-Me analog, are about 10 times more potent than pamidronate. Extending one of the N-Me groups of olpadronate to a pentyl substituent leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most potent close analog of pamidronate. Even slightly better antiresorptive potency is achieved with derivs. having a Ph group linked via a short aliph. tether of three to four atoms to nitrogen, the second substituent being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most potent BPs are found in the series contg. a heteroarom. moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal **bisphosphonate** unit. **Zoledronic** acid (6i), the most potent deriv., has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after s.c. administration. It not only shows by far the highest therapeutic ratio when comparing resorption inhibition with undesired inhibition of bone mineralization but also exhibits superior renal tolerability. **Zoledronic** acid (6i) has thus been selected for clin. development under the registered trade name Zometa. The results of the clin. trials indicate that low doses are both efficacious and safe for the treatment of **tumor**-induced hypercalcemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis.

IT Methyl group
Phenyl group
Structure-activity relationship
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Osteoclast
(bone resorption; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Bone
(resorption, osteoclastic; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Osteoporosis
(therapeutic agents, postmenopausal; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 29712-30-9P 32545-72-5P 56152-35-3P 63132-38-7P 63132-40-1P
63161-30-8P **66376-36-1P**, Alendronate 67242-32-4P
79778-41-9P, Neridronate 86235-67-8P 89732-96-7P
104261-68-9P **114084-78-5P**, Ibandronate 114084-82-1P
114119-81-2P 116162-22-2P 116786-78-8P 116786-79-9P 116786-83-5P
116786-85-7P 116786-88-0P 116786-89-1P 116786-90-4P 118054-12-9P
118054-15-2P 118054-16-3P 118054-18-5P 118054-19-6P 118054-20-9P
118054-23-2P 118054-31-2P 118054-32-3P 118054-33-4P 118054-41-4P
118054-42-5P 118054-51-6P 118054-52-7P **118072-93-8P**
118694-16-9P 121368-58-9P, Olpadronate **124351-85-5P**
124369-71-7P 124369-72-8P 124369-73-9P 124369-77-3P 124369-80-8P
124369-81-9P 124369-83-1P 125946-91-0P 128202-57-3P 129951-00-4P
129951-01-5P 129951-02-6P 131654-39-2P 131654-40-5P 131654-41-6P
131654-58-5P 132423-84-8P 132423-86-0P 132423-87-1P 132423-88-2P
132423-89-3P 132423-90-6P 132423-92-8P 132423-94-0P 132423-95-1P
132423-96-2P 132423-97-3P 132423-98-4P 132423-99-5P 132424-00-1P
132424-01-2P 134579-54-7P 134579-55-8P 134579-56-9P 136671-90-4P
142830-99-7P 149226-80-2P 154188-60-0P 183446-90-4P 183446-98-2P
209002-31-3P 209002-32-4P 459870-45-2P 459870-46-3P 459870-47-4P
459870-48-5P 459870-49-6P 459870-50-9P 459870-51-0P 459870-52-1P
459870-53-2P 459870-54-3P 459870-55-4P 459870-56-5P 459870-57-6P
459870-58-7P 459870-59-8P 459870-60-1P 459870-61-2P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT **40391-99-9** 41003-10-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 96-50-4, 2-Aminothiazole 936-44-7, 3-Phenylpyrrolidine 1008-73-7 1660-94-2, Tetraethyl methylenebisphosphonate 3612-20-2, 1-Benzylpiperidin-4-one 4584-46-7, 2-Chloroethyldimethylamine hydrochloride 6646-51-1, 2-Amino-1-methylimidazole 7305-71-7, 2-Amino-5-methylthiazole 7552-07-0, 1,2,4-Thiadiazol-5-amine 16270-07-8 21722-08-7 22944-67-8 41441-40-1 149692-49-9 459870-63-4 459870-64-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 2302-39-8P, 4,5-Dimethylimidazole 17334-08-6P 120418-62-4P 183446-91-5P 183446-95-9P 459870-65-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:526926 CAPLUS
DOCUMENT NUMBER: 138:100192
TITLE: Pharmacologic profile of **zoledronic** acid: A highly potent inhibitor of bone resorption
AUTHOR(S): Green, Jonathan R.; Rogers, Michael J.
CORPORATE SOURCE: Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Drug Development Research (2002), 55(4), 210-224
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Bisphosphonates** are effective in treating benign and malignant skeletal diseases characterized by enhanced osteoclastic bone resorption (i.e., osteoporosis, Paget's disease, **tumor**-induced osteolysis). The nitrogen-contg. **bisphosphonate** pamidronate is currently the std. treatment for hypercalcemia of malignancy (HCM) and skeletal complications of bone metastases. **Zoledronic** acid, a novel nitrogen-contg. **bisphosphonate** with an imidazole substituent, has demonstrated more potent inhibition of osteoclast-mediated bone resorption than all other **bisphosphonates**, including pamidronate, in both in vitro and in vivo preclin. models. **Zoledronic** acid inhibited ovariectomy-induced bone loss in adult monkeys and rats, and long-term treatment prevented skeletal turnover and subsequent bone loss, reduced cortical porosity, and increased mech. strength. **Zoledronic** acid also significantly inhibited bone loss assocd. with **arthritis**, bone metastases, and prosthesis loosening. The increased potency of **zoledronic** acid vs. pamidronate has been demonstrated clin.: **zoledronic** acid (4 or 8 mg iv) was superior to pamidronate (90 mg iv) in normalizing cor. serum calcium in patients with HCM. In patients with bone metastases, low doses of **zoledronic** acid (.ltoreq. 2 mg) suppressed bone resorption markers .ltoreq. 50% below baseline, whereas pamidronate 90 mg yielded only 20 to 30% suppression. Importantly, the increased potency of **zoledronic** acid is not assocd. with an increased incidence of local (bone) or systemic adverse events. **Zoledronic** acid does

not impair bone mineralization and, compared with pamidronate, has a greater renal and intestinal tolerability therapeutic index. Thus, based on preclin. assays and clin. data, **zoledronic** acid is the most potent **bisphosphonate** tested to date. Given its potency and excellent safety profile, **zoledronic** acid is now poised to become the new std. of treatment for HCM and metastatic bone disease.

IT Human
(bone resorption inhibitor, **zoledronic** acid)

IT Bone, **neoplasm**
(metastasis; bone resorption inhibitor, **zoledronic** acid)

IT Bone
(resorption, inhibitors; bone resorption inhibitor, **zoledronic** acid)

IT 13598-36-2D, Phosphonic acid, alkylidinebis- derivs.
RL: PAC (Pharmacological activity); BIOL (Biological study)
(bone resorption inhibitor, **zoledronic** acid)

IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bone resorption inhibitor, **zoledronic** acid)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; bone resorption inhibitor, **zoledronic** acid)

REFERENCE COUNT: 105 THERE ARE 105 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:486034 CAPLUS
DOCUMENT NUMBER: 138:66277
TITLE: The **bisphosphonate zoledronic** acid impairs membrane localization and induces cytochrome c release in breast **cancer** cells
AUTHOR(S): Senaratne, S. G.; Mansi, J. L.; Colston, K. W.
CORPORATE SOURCE: Department of Oncology, Gastroenterology, Endocrinology and Metabolism, St. George's Hospital Medical School, London, SW17 0RE, UK
SOURCE: British Journal of Cancer (2002), 86(9), 1479-1486
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Forced expression of the antiapoptotic protein bcl-2 attenuated **zoledronic** acid-induced loss of cell viability and induction of DNA fragmentation in human breast **cancer** MDA-MB-231 cells. **Zoledronic** acid-mediated apoptosis was assocd. with a time- and concn.-related release of mitochondrial cytochrome c into the cytosol in two cell lines. Rescue of the cells by preincubation with a caspase-3-selective inhibitor and demonstration of procaspase-3 cleavage products by immunoblotting suggested that at least one of the caspases activated in response to **zoledronic** acid treatment is caspase-3. In both MDA-MB-231 and MCF-7 breast **cancer** cells, **zoledronic** acid impaired membrane localization of Ras, indicating reduced prenylation of this protein. These observations demonstrate that **zoledronic** acid-mediated apoptosis is assocd. with cytochrome c release and consequent caspase activation. This process may be initiated by inhibition of the enzymes in the mevalonate pathway, leading to impaired prenylation of key intracellular proteins, including Ras.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-2; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release

in human breast **cancer** cells in relation to expression of)

IT Cell membrane
Human
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Ras proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Apoptosis
Signal transduction, biological
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells in relation to)

IT Antitumor agents
(breast **cancer**; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Mammary gland
(**neoplasm**, inhibitors; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT 9007-43-6, Cytochrome c, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT 169592-56-7, Caspase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells in relation to)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; **zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:429803 CAPLUS
DOCUMENT NUMBER: 137:41697
TITLE: **Zoledronic** acid versus pamidronate as palliative therapy in **cancer** patients: A Canadian time and motion analysis
AUTHOR(S): Dranitsaris, George; Castel, Liana D.; Baladi, Jean Francois; Schulman, Kevin A.
CORPORATE SOURCE: Department of Molecular Biology, Ontario Cancer Institute and Princess Margaret Hospital, Toronto, ON, M5G 2M9, Can.
SOURCE: Journal of Oncology Pharmacy Practice (2001), 7(1),

27-33
CODEN: JOPPFI; ISSN: 1078-1552
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pamidronate was an important advance in the palliative treatment of patients with **cancer**. However, pamidronate must be infused over at least 2 h in most patients. **Zoledronic** acid represents the next-generation **bisphosphonate** with a potential for improved efficacy in the palliative care setting. One important advantage of **zoledronic** acid is that it can be administered over a 15-min infusion. To measure the overall efficiency of **zoledronic** acid as compared with pamidronate in the outpatient setting, a USA microcosting model was adapted to Canadian inputs. Time and motion data were collected from six patients being treated with **zoledronic** acid or pamidronate in three USA outpatient **cancer** clinics. Resource use and time impact on outpatient clin. staff were reanalyzed using Canadian cost ests. This included the evaluation of fixed, variable, and labor costs obtained from Canadian sources. The manufacturer provided drug costs. The base case anal. assumed a 5300-ft2 out-patient chemotherapy clinic with eight infusion chairs designated for **bisphosphonate** administration in the province of Ontario. Mean treatment times in the original USA data collected were 2 h, 52 min for pamidronate, and 1 h, 6 min for **zoledronic** acid (a difference of 1 h, 46 min). In the Canadian version of the microcosting model, the overall treatment cost was Can$673 for pamidronate and Can$682 for **zoledronic** acid (2001 Canadian dollars). Findings suggest that the shorter **zoledronic** acid infusion time would allow an addnl. 27 **bisphosphonate** patients to be treated per day. Alternatively, approx. one addnl. hour of chair time could be made available with each zoledonic acid infusion. Sensitivity analyses revealed that (a) the base case results were consistent when geog. region was varied, and (b) the shorter the infusion time for **zoledronic** acid relative to pamidronate, the lesser the cost difference and more patients could be treated daily. In conclusion, **zoledronic** acid may enhance the overall efficiency of outpatient chemotherapy clinics by reducing patient waiting time for **bisphosphonate** administration. These benefits would be obtained at an incremental cost of Can$9 per infusion.

IT Bone, disease
(fracture; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

IT **Neoplasm**
(humoral hypercalcemia of malignancy; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

IT Bone, **neoplasm**
(metastasis, pain; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

IT **Neoplasm**
Simulation and Modeling, biological
(**zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

IT **40391-99-9 118072-93-8, Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:428720 CAPLUS
DOCUMENT NUMBER: 137:746
TITLE: Use of **bisphosphonates** for pain treatment
INVENTOR(S): Fox, Alyson; Green, Jonathan; O'Reilly, Terence; Urban, Laszlo; Walker, Katharine
PATENT ASSIGNEE(S): Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002043738	A2	20020606	WO 2001-EP13836	20011127
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
AU 2002017061	A5	20020611	AU 2002-17061	20011127

PRIORITY APPLN. INFO.: GB 2000-29111 A 20001129
WO 2001-EP13836 W 20011127

OTHER SOURCE(S): MARPAT 137:746

AB A method for the treatment of pain, in particular antinociceptive or anti-allodynic treatment of pain, in a patient in need of such treatment, e.g. a patient with osteoporosis or osteopenia, a **tumor** patient, or a patient suffering from an **inflammatory** disease, comprises administering an effective amt. of a **bisphosphonate**, e.g. **zoledronic** acid or salts or hydrates thereof, to the patient.

IT Pain
Skin, disease
(allodynia; **bisphosphonates** for pain treatment)
IT Analgesics
(**bisphosphonates** for pain treatment)
IT Drug delivery systems
(capsules; **bisphosphonates** for pain treatment)
IT Mammary gland
(carcinoma, MRMZ-1 cells, bone pain assoc. with; **bisphosphonates** for pain treatment)
IT **Inflammation**
(**inflammatory** pain; **bisphosphonates** for pain treatment)
IT Drug delivery systems
(infusions, i.v.; **bisphosphonates** for pain treatment)
IT **Neoplasm**
(metastasis, pain assocd. with; **bisphosphonates** for pain treatment)
IT Nerve, disease
(neuropathy, neuropathic pain; **bisphosphonates** for pain treatment)
IT **Neoplasm**
Osteoarthritis

Osteoporosis
Rheumatoid **arthritis**
(pain assocd. with; **bisphosphonates** for pain treatment)

IT Bone
(pain; **bisphosphonates** for pain treatment)

IT Drug delivery systems
(transdermal; **bisphosphonates** for pain treatment)

IT 197313-76-1, **NE 10244**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10244**; **bisphosphonates** for pain treatment)

IT 183490-29-1, **NE 10446**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10446**; **bisphosphonates** for pain treatment)

IT 930-73-4 **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **40391-99-9**, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8 66376-36-1**, Alendronic acid **79778-41-9 89987-06-4**, Tiludronic acid **105462-24-6**, Risedronic acid 105462-24-6D, Risedronic acid, N-methylpyridinium salts 112855-84-2 **114084-78-5** 118054-32-3 **118072-93-8**, **Zoledronic** acid 125946-91-0 **125946-92-1**, EB 1053 132423-94-0 132508-02-2 138844-81-2, BM 21.0955 **180064-38-4** 433685-76-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** for pain treatment)

L10 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:868193 CAPLUS
DOCUMENT NUMBER: 136:11141
TITLE: Intravenous administration of a **bisphosphonate**
INVENTOR(S): Seaman, John J.; Sigg, Juergen; Schran, Horst
PATENT ASSIGNEE(S): Novartis A.-G., Switz.
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001089494	A2	20011129	WO 2001-US14886	20010509
WO 2001089494	A3	20020523		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-12209 A 20000519

AB A method of i.v. administering a **bisphosphonate** to a patient in need of **bisphosphonate** treatment comprising i.v. administering 4 mg of **zoledronic** acid or a pharmaceutically acceptable salt thereof over a period of 15 min to a patient in need of said treatment.

IT Antitumor agents
(bone, metastasis; i.v. administration of a **bisphosphonate**)
IT **Neoplasm**
(humoral hypercalcemia of malignancy; i.v. administration of a **bisphosphonate**)
IT Bone, **neoplasm**
(metastasis, inhibitors; i.v. administration of a **bisphosphonate**)
IT Drug delivery systems
(solns., i.v.; i.v. administration of a **bisphosphonate**)
IT 7440-70-2, Calcium, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hypercalcemia; i.v. administration of a **bisphosphonate**)
IT 17341-25-2, Sodium ion, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. administration of a **bisphosphonate**)
IT **118072-93-8**, **Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. administration of a **bisphosphonate**)

L10 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:829626 CAPLUS
DOCUMENT NUMBER: 137:57065
TITLE: Early detection of bone metastases in a murine model using fluorescent human breast **cancer** cells: application to the use of the **bisphosphonate** **zoledronic** acid in the treatment of osteolytic lesions
AUTHOR(S): Peyruchaud, Olivier; Winding, Bent; Pecheur, Isabelle; Serre, Claire-Marie; Delmas, Pierre; Clezardin, Philippe
CORPORATE SOURCE: INSERM Research Unit 403, Faculte de Medecine Laennec, Lyon, Fr.
SOURCE: Journal of Bone and Mineral Research (2001), 16(11), 2027-2034
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A very common metastatic site for human breast **cancer** is bone. The traditional bone metastasis model requires human MDA-MB-231 breast carcinoma cell inoculation into the left heart ventricle of nude mice. MDA-MB-231 cells usually develop osteolytic lesions 3-4 wk after intracardiac inoculation in these animals. Here, the authors report a new approach to study the formation of bone metastasis in animals using breast carcinoma cells expressing the bioluminescent jellyfish protein (green fluorescent protein [GFP]). The authors first established a subclone of MDA-MB-231 cells by repeated in vivo passages in bone using the heart injection model. On stable transfection of this subclone with an expression vector for GFP and subsequent inoculation of GFP-expressing **tumor** cells (B02/GFP.2) in the mouse tail vein, B02/GFP.2 cells displayed a unique predilection for dissemination to bone. Externally fluorescence imaging of live animals allowed the detection of fluorescent bone metastases approx. 1 wk before the occurrence of radiol. distinctive osteolytic lesions. The no., size, and intensity of fluorescent bone metastases increased progressively with time and was indicative of breast **cancer** cell progression within bone. Histol. examn. of fluorescent long bones from B02/GFP.2-bearing mice revealed the occurrence of profound bone destruction. Treatment of B02/GFP.2-bearing mice with the **bisphosphonate** **zoledronic** acid markedly inhibited

the progression of established osteolytic lesions and the expansion of breast **cancer** cells within bone. Overall, this new bone metastasis model of breast **cancer** combining both fluorescence imaging and radiog. should provide an invaluable tool to study the effectiveness of pharmaceutical agents that could suppress **cancer** colonization in bone.

IT Antitumor agents
(bone; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Disease models
Human
(early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Imaging
(fluorescent; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Proteins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(green fluorescent; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Bone, **neoplasm**
(metastasis; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Mammary gland
(**neoplasm**; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Bone, disease
(osteolysis; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:582508 CAPLUS
DOCUMENT NUMBER: 135:339158
TITLE: Safety and efficacy of **bisphosphonates** beyond 24 months in **cancer** patients
AUTHOR(S): Ali, S. M.; Esteva, F. J.; Hortobagyi, G.; Harvey, H.; Seaman, J.; Knight, R.; Costa, L.; Lipton, A.
CORPORATE SOURCE: M.S. Hershey Medical Center, Hershey, PA, USA
SOURCE: Journal of Clinical Oncology (2001), 19(14), 3434-3437

CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bisphosphonate** therapy has decreased the risk of skeletal complications assocd. with osteolytic bone lesions in patients with breast **cancer** and multiple myeloma. The large prospective studies have used 21 to 24 mo of treatment. We studied the safety and efficacy of **bisphosphonates** in a subset of patients who received therapy for more than 24 mo. Patients who received **bisphosphonates** (pamidronate or **zoledronic** acid) were identified. Data on skeletal events and lab. parameters were gathered by chart review. We studied 22 patients who received i.v. pamidronate or **zoledronic** acid for a duration of 3.6 yr (range, 2.2 to 6.0 yr). Prolonged therapy was well tolerated. No significant calcium, phosphorus, electrolyte, or WBC count abnormalities were encountered. There was a clin. insignificant decrease in Hb and platelet count and an increase in creatinine in these patients. The fracture rate beyond 2 yr was no greater than during the first 2 yr of treatment. There were no stress fractures of long bones with prolonged therapy. Prolonged treatment with the potent **bisphosphonates** pamidronate and **zoledronic** acid seems to be well tolerated and should be studied in prospective, randomized studies to document prolonged skeletal efficacy.

IT Multiple myeloma
Skeleton
(efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT Mammary gland
(**neoplasm**; efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT 57248-88-1, Aredia **118072-93-8**, Zometa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:418592 CAPLUS
DOCUMENT NUMBER: 136:160948
TITLE: The **bisphosphonate, zoledronic** acid, induces apoptosis of breast **cancer** cells: Evidence for synergy with paclitaxel
AUTHOR(S): Jagdev, S. P.; Coleman, R. E.; Shipman, C. M.; Rostami-H, A.; Croucher, P. I.
CORPORATE SOURCE: YCR Department of Clinical Oncology, Weston Park Hospital, Sheffield, UK
SOURCE: British Journal of Cancer (2001), 84(8), 1126-1134
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bisphosphonates** are well established in the management of breast-**cancer**-induced bone disease. Recent studies have

suggested that these compds. are effective in preventing the development of bone metastases. However, it is unclear whether this reflects an indirect effect via an inhibition of bone resorption or a direct antitumor effect. The breast **cancer** cell lines, MCF-7 and MDA-MB-231 cells were treated with increasing concns. of the **bisphosphonate**, **zoledronic** acid, for varying time periods, in the presence or absence of paclitaxel. The effects of **zoledronic** acid were detd. by assessing cell no. and rate of apoptosis by evaluating changes in nuclear morphol. and using a fluorescence nick translation assay. **Zoledronic** acid caused a dose- and time-dependent decrease in cell no. ($P < 0.001$) and a concomitant increase in **tumor** cell apoptosis ($P < 0.005$). Short-term exposure to **zoledronic** acid was sufficient to cause a significant redn. in cell no. and increase in apoptosis ($P < 0.05$). These effects could be prevented by incubation with geranyl geraniol, suggesting that **zoledronic** acid-induced apoptosis is mediated by inhibiting the mevalonate pathway. Treatment with **zoledronic** acid and clin. achievable concns. of paclitaxel resulted in a 4-5-fold increase in **tumor** cell apoptosis ($P < 0.02$). Isobologram anal. revealed synergistic effects on **tumor** cell no. and apoptosis when **zoledronic** acid and paclitaxel were combined. Short-term treatment with **zoledronic** acid, which closely resembles the clin. setting, has a clear antitumor effect on breast **cancer** cells. Importantly, the commonly used anti-neoplastic agent, paclitaxel, potentiates the antitumor effects of **zoledronic** acid. These data suggest that, in addn. to inhibiting bone resorption, **zoledronic** acid has a direct antitumor activity on breast **cancer** cells in vitro.

IT Antitumor agents
(mammary gland; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Mammary gland
(**neoplasm**, inhibitors; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Drug interactions
(synergistic; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Apoptosis
(**zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT 33069-62-4, Paclitaxel **118072-93-8**, **Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:307374 CAPLUS
DOCUMENT NUMBER: 135:220794
TITLE: A phase I dose-ranging trial of monthly infusions of **zoledronic** acid for the treatment of osteolytic bone metastases
AUTHOR(S): Berenson, James R.; Vescio, Robert A.; Rosen, Lee S.; VonTeichert, Joseph M.; Woo, Margie; Swift, Regina; Savage, Allison; Givant, Elise; Hupkes, Mieke; Harvey, Harold; Lipton, Allan
CORPORATE SOURCE: Division of Hematology and Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, 90048, USA
SOURCE: Clinical Cancer Research (2001), 7(3), 478-485
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** are potent inhibitors of bone resorption and provide a therapeutic benefit for patients with bone metastases. **Zoledronic** acid is a highly potent, nitrogen-contg. **bisphosphonate**. In the present trial, we assessed the safety and tolerability of increasing doses of **zoledronic** acid and its effects on urinary markers of bone resorption in **cancer** patients with bone metastases. Fifty-nine **cancer** patients with bone metastases were enrolled sequentially into one of 8 treatment groups in the core protocol. Each patient received a 5-min i.v. infusion of 0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, or 8 mg **zoledronic** acid monthly for 3 mo. Patients were monitored for clin. findings, adverse events, electrocardiograms, markers of bone resorption, as well as routine hematol., blood chemistries, and urinalysis. Thirty patients who demonstrated a radiog. response to treatment or stable disease in the core protocol were enrolled in a humanitarian extension protocol and continued to receive monthly infusions. **Zoledronic** acid was well tolerated at all dose levels. Adverse events reported by >10% of patients included skeletal pain, nausea, fatigue, upper respiratory tract infection, constipation, headache, diarrhea, and fever. Three patients in the core protocol and one patient in the extension protocol experienced grade 3 skeletal pain, "flulike" symptoms, or hypophosphatemia, which were possibly related to treatment; all recovered completely. Adverse events were reported with similar frequency across all of the dosage groups. **Zoledronic** acid resulted in sustained, dose-dependent decreases in urinary markers of bone resorption. **Zoledronic** acid was safe and well tolerated and demonstrated potent inhibition of bone resorption.
IT Bone, **neoplasm**
(metastasis; increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
IT Bone
(resorption, inhibitors; increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
IT **118072-93-8, zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:278266 CAPLUS
DOCUMENT NUMBER: 135:189951
TITLE: **Zoledronic** acid reduces skeletal-related events in patients with osteolytic metastases: A double-blind, randomized dose-response study
AUTHOR(S): Berenson, James R.; Rosen, Lee S.; Howell, Anthony; Porter, Lester; Coleman, Robert E.; Morley, Walter; Dreicer, Robert; Kuross, Steven A.; Lipton, Allan; Seaman, John J.
CORPORATE SOURCE: Cedars-Sinai Medical Center, Los Angeles, CA, USA
SOURCE: Cancer (New York, NY, United States) (2001), 91(7), 1191-1200
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study evaluated the dose-response relation for **zoledronic**

acid, a new generation high-potency **bisphosphonate**, given as a 5-min infusion in patients with malignant osteolytic disease. Two-hundred eighty patients with osteolytic lesions due to metastatic breast carcinoma or multiple myeloma were randomized to double-blind treatment with 0.4, 2.0, or 4.0 mg of **zoledronic** acid or 90 mg pamidronate. The primary efficacy endpoint was the proportion of patients receiving radiation to bone. Other skeletal-related events, bone mineral d. (BMD), bone markers, Eastern Cooperative Oncol. Group performance status, pain and analgesic scores, and safety also were evaluated. **Zoledronic** acid at doses of 2.0 and 4.0 mg and pamidronate at a dose of 90 mg each significantly reduced the need for radiation therapy to bone ($P < 0.05$) in contrast with 0.4 mg **zoledronic** acid, which did not. Skeletal-related events of any kind, pathol. fractures, and hypercalcemia also occurred less frequently in patients treated with 2.0 or 4.0 mg **zoledronic** acid or pamidronate than with 0.4 mg **zoledronic** acid. Increases in lumbar spine BMD (6.2-9.6%) and decreases in the bone resorption marker N-telopeptide (range, -37.1 to -60.8%) were obsd. for all treatment groups. Skeletal pain, fatigue, nausea, vomiting, and headache were the most commonly reported adverse events. Adverse events were similar in nature and frequency with **zoledronic** acid and pamidronate. A 5-min infusion of 2.0-4.0 mg **zoledronic** acid was at least as effective as a 2-h 90-mg pamidronate infusion in treatment of osteolytic metastases. A 0.4-mg dose of **zoledronic** acid was significantly less effective. Both **zoledronic** acid and pamidronate were well tolerated.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:82572 CAPLUS
DOCUMENT NUMBER: 135:132357
TITLE: A phase I, open label, dose ranging trial of intravenous bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease
AUTHOR(S): Berenson, James R.; Vescio, Robert; Henick, Kathryn; Nishikubo, Carol; Retting, Matthew; Swift, Regina A.; Conde, Francisco; Von Teichert, Joseph M.
CORPORATE SOURCE: Department of Medicine, Cedars Sinai Medical Center, Los Angeles, CA, 90048, USA
SOURCE: Cancer (New York) (2001), 91(1), 144-154
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone metastases typically are assocd. with osteolytic bone destruction, resulting in bone pain, pathol. fractures, spinal cord compression, and hypercalcemia. **Bisphosphonates** are potent inhibitors of normal and pathol. bone resorption and represent a significant therapeutic improvement in the management of patients with lytic bone metastases. **Zoledronic** acid is a new generation, highly potent, nitrogen-contg. **bisphosphonate** that to the authors knowledge is the most potent inhibitor of bone resorption currently in clin. trials.

The objectives of the current study were to assess the safety and tolerability of increasing doses of **zoledronic** acid and to det. its activity with respect to reducing biochem. markers of bone resorption in **cancer** patients with bone metastases. Forty-four **cancer** patients with bone metastases or primary bone lesions were enrolled sequentially into 1 of 5 fixed ascending-dose treatment groups. Each patient received a single i.v. bolus injection of 1, 2, 4, 8, or 16 mg of **zoledronic** acid over 30-60 s. Patients were monitored for 8 wk for the evaluation of clin. findings, adverse events, vital signs, electrocardiograms, markers of bone resorption, and urinary N-acetyl-.beta.-D-glucosaminidase. **Zoledronic** acid was safe and well tolerated at all dose levels tested. Commonly reported adverse events included bone pain, fever, anorexia, constipation, and nausea, which were experienced by a similar proportion of patients in each treatment group. Seven patients reported serious adverse events, none of which appeared to be related to the study drug. **Zoledronic** acid effectively suppressed biochem. markers of bone resorption, including the highly specific markers N-telopeptide and deoxypyridinoline, for up to 8 wk in the 2-16-mg dose groups and for a shorter duration in the 1-mg group. In the current study, **zoledronic** acid was safe and well tolerated and demonstrated potent inhibition of bone resorption. The authors believe it may improve the treatment of metastatic bone disease.

IT Peptides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(N-Telopeptide; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT Bone, **neoplasm**
(metastasis; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT Bone
(resorption, inhibitors; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT 83462-55-9, Deoxypyridinoline
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT 9012-33-3, N-Acetyl-.beta.-D-glucosaminidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(urinary; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:51861 CAPLUS
DOCUMENT NUMBER: 135:131487
TITLE: Myeloma - the therapeutic challenge
AUTHOR(S): Berenson, James R.
CORPORATE SOURCE: Cedars-Sinai Medical Center, UCLA School of Medicine,

SOURCE: Los Angeles, CA, USA
Medizinische Klinik (Muenchen) (2000), 95(Suppl. 2), 19-21
CODEN: MEKLA7; ISSN: 0723-5003
PUBLISHER: Urban & Vogel Medien und Medizin Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 20 refs. Bone loss, the major clin. manifestation of multiple myeloma, often leads to pathol. fractures, spinal cord compression, hypercalcemia and bone pain. Analgesics, surgery and radiotherapy may effectively palliate patients with complications from myeloma bone disease, but cannot slow the progressive bone loss. Chemotherapy may reduce **tumor** burden but has little impact on the underlying bone disease. A dramatic change was the demonstration that i.v. pamidronate could reduce skeletal complications. Importantly, because **bisphosphonates** lack significant bone marrow suppressive effects they can be administered to other cytotoxic therapy. Lab. studies show the improved potency of the 3rd-generation **bisphosphonate** **zoledronic** acid in its anti-bone resorptive as well as anti-myeloma effects. Phase-I and -II studies evaluating **zoledronic** acid in myeloma patients show marked and sustained inhibition of bone resorption markers. The randomized studies evaluating **zoledronic** acid have demonstrated its superiority to pamidronate in overcoming **tumor**-induced hypercalcemia. Results of ongoing phase-III studies will det. its relative safety and efficacy compared to pamidronate.

IT Antitumor agents
(myeloma; therapeutic challenges in treating multiple Myeloma)

IT Bone
(resorption; therapeutic challenges in treating multiple Myeloma)

IT Multiple myeloma
(therapeutic challenges in treating multiple Myeloma)

IT **118072-93-8**, **Zoledronic** acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic challenges in treating multiple Myeloma)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:841963 CAPLUS
DOCUMENT NUMBER: 134:524
TITLE: Methods and pharmaceutical compositions using **bisphosphonates** for the treatment of **angiogenesis**
INVENTOR(S): Okuno, Tetsuji; Green, Jonathan; Wood, Jeanette Marjorie
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071104	A2	20001130	WO 2000-EP4562	20000519
WO 2000071104	A3	20010719		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1178810	A2	20020213	EP 2000-936760	20000519
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010808	A	20020827	BR 2000-10808	20000519
JP 2003500352	T2	20030107	JP 2000-619411	20000519
NO 2001005638	A	20020115	NO 2001-5638	20011119
US 2002142996	A1	20021003	US 2001-989577	20011120

PRIORITY APPLN. INFO.:

GB 1999-11926	A	19990521
GB 1999-25131	A	19991022
WO 2000-EP4562	W	20000519

AB A method is provided for the treatment of **angiogenesis** in a patient in need of such treatment, e.g. a **tumor** patient or a patient suffering from an **inflammatory** disease, which comprises administering, preferably via an intra-arterial route, an effective amt. of a **bisphosphonate**, e.g. pamidronic acid or **zoledronic** acid or salts or hydrates thereof, to the patient.

IT Animal cell line
(HUVEC; **bisphosphonate** for **angiogenesis** treatment)

IT **Angiogenesis** inhibitors
Anti-**inflammatory** agents
Anti-ischemic agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Cell migration
(**bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(capsules; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(carcinoma, A431 cell; **bisphosphonate** for **angiogenesis** treatment)

IT Blood vessel
(endothelium; **bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(freeze-dried; **bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(infusions, i.v.; **bisphosphonate** for **angiogenesis** treatment)

IT Heart, disease
(**ischemia**; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(lung, metastasis, from breast; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(mammary gland, metastasis, to lung; **bisphosphonate** for **angiogenesis** treatment)

IT Lung, **neoplasm**
(metastasis, inhibitors, from breast; **bisphosphonate** for **angiogenesis** treatment)

IT Mammary gland
(metastasis, inhibitors, to lung; **bisphosphonate** for **angiogenesis** treatment)
IT Antitumor agents
(metastasis; **bisphosphonate** for **angiogenesis** treatment)
IT Proliferation inhibition
(proliferation inhibitors; **bisphosphonate** for **angiogenesis** treatment)
IT Drug delivery systems
(transdermal; **bisphosphonate** for **angiogenesis** treatment)
IT 132508-02-2, U 81581
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(U 81581; **bisphosphonate** for **angiogenesis** treatment)
IT 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate** for **angiogenesis** treatment)
IT **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid
13598-36-2D, Phosphonic acid, **bisphosphonates 40391-99-9**
, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8**
66376-36-1, Alendronic acid **79778-41-9**
89987-06-4, Tiludronic acid **105462-24-6**, Risedronic acid
105462-24-6D, Risedronic acid, N-Me pyridinium salts 112855-84-2, FR 78844 **114084-78-5**, Ibandronic acid **118072-93-8**,
Zoledronic acid 118072-93-8D, mixed sodium salts 125946-91-0
125946-92-1, EB 1053 132423-94-0 138844-81-2, BM 21.0955
180064-38-4, YM 529 183490-29-1, **NE 10446**
197313-76-1, **NE 10244**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate** for **angiogenesis** treatment)

=>

L15 ANSWER 4 OF 14 USPATFULL

ACCESSION NUMBER:	2002:329505 USPATFULL
TITLE:	Method of treating restenosis using **bisphosphonate** nanoparticles
INVENTOR(S):	Golomb, Gershon, Efrat, ISRAEL Danenberg, Haim, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002187184	A1	20021212
APPLICATION INFO.:	US 2002-126248	A1	20020419 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-743705, filed on 22 Mar 2001, PENDING A 371 of International Ser. No. WO 1999-IL387, filed on 14 Jul 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-125336	19980714

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MORGAN & FINNEGAN, L.L.P., 345 Park Avenue, New York, NY, 10154-0053
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Page(s)
LINE COUNT:	1265

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating or preventing restenosis by administering to an individual an effective amount of an active ingredient comprising a **bisphosphonate** particle or a **bisphosphonate** particulate. The **bisphosphonate** may be encapsulated, embedded or adsorbed within the particle, dispersed uniformly in the polymer matrix, adsorbed on the particle surface, or in combination of any of these forms. The particles include liposomes or inert polymeric particles, such as microcapsules, nanocapsules, nanoparticles, nanospheres, or microparticles. The particulates include any suspended or dispersed form of the **bisphosphonate** which is not encapsulated, entrapped, or adsorbed within a polymeric particle. The particulates include suspended or dispersed colloids, aggregates, flocculates, insoluble salts and insoluble complexes of the active ingredient. The active ingredient effects restenosis by inhibiting the growth and proliferation of the cell types involved in the restenotic cascade, such as macrophages/monocytes, fibroblasts and smooth-muscle cells.

ACCESSION NUMBER: 2003:17932 USPATFULL
TITLE: Method of inhibiting restenosis using **bisphosphonates**
INVENTOR(S): Golomb, Gershon, Efrat, ISRAEL
Danenberg, Haim, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003013686	A1	20030116
APPLICATION INFO.:	US 2002-160207	A1	20020530 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-126248, filed on 19 Apr 2002, PENDING Continuation-in-part of Ser. No. US 2001-743705, filed on 22 Mar 2001, PENDING A 371 of International Ser. No. WO 1999-IL387, filed on 14 Jul 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-125336	19980714

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN & FINNEGAN, L.L.P., 345 Park Avenue, New York, NY, 10154-0053
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1039

AB A method of inhibiting the activity or production of cytokines or growth factors associated with vascular restenosis, by administering to an individual an effective amount of an active ingredient comprising a **bisphosphonate** particle or a **bisphosphonate** particulate. The **bisphosphonate** may be encapsulated, embedded or adsorbed within the particle, dispersed uniformly in the polymer matrix, adsorbed on the particle surface, or in combination of any of these forms. The particles include liposomes or inert polymeric particles, such as microcapsules, nanocapsules, nanoparticles, nanospheres, or microparticles. The particulates include any suspended or dispersed form of the **bisphosphonate** which is not encapsulated, entrapped, or adsorbed within a polymeric particle. The particulates include suspended or dispersed colloids, aggregates, flocculates, insoluble salts and insoluble complexes of the active ingredient. The cytokines and growth factors include, but are not limited to interleukin 1-.beta., matrix metalloproteinase-2, and platelet-derived growth factor .beta. (PDGF.beta.).

11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:841963 CAPLUS
DOCUMENT NUMBER: 134:524
TITLE: Methods and pharmaceutical compositions using bisphosphonates for the treatment of **angiogenesis**
INVENTOR(S): Okuno, Tetsuji; Green, Jonathan; Wood, Jeanette Marjorie
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071104	A2	20001130	WO 2000-EP4562	20000519
WO 2000071104	A3	20010719		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1178810	A2	20020213	EP 2000-936760	20000519
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010808	A	20020827	BR 2000-10808	20000519
JP 2003500352	T2	20030107	JP 2000-619411	20000519
NO 2001005638	A	20020115	NO 2001-5638	20011119
US 2002142996	A1	20021003	US 2001-989577	20011120

PRIORITY APPLN. INFO.:
GB 1999-11926 A 19990521
GB 1999-25131 A 19991022
WO 2000-EP4562 W 20000519

AB A method is provided for the treatment of **angiogenesis** in a patient in need of such treatment, e.g. a **tumor** patient or a patient suffering from an **inflammatory** disease, which comprises administering, preferably via an **intra-arterial** route, an effective amt. of a bisphosphonate, e.g. pamidronic acid or zoledronic acid or salts or hydrates thereof, to the patient.

IT Animal cell line
(HUVEC; bisphosphonate for **angiogenesis** treatment)
IT **Angiogenesis** inhibitors
Anti-**inflammatory** agents
Anti-ischemic agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Cell migration
(bisphosphonate for **angiogenesis** treatment)
IT Drug delivery systems
(capsules; bisphosphonate for **angiogenesis** treatment)
IT Antitumor agents
(carcinoma, A431 cell; bisphosphonate for **angiogenesis** treatment)
IT Blood vessel

(endothelium; bisphosphonate for **angiogenesis** treatment)
IT Drug delivery systems
(freeze-dried; bisphosphonate for **angiogenesis** treatment)
IT Drug delivery systems
(infusions, i.v.; bisphosphonate for **angiogenesis** treatment)
IT Heart, disease
(**ischemia**; bisphosphonate for **angiogenesis** treatment)
IT Antitumor agents
(lung, metastasis, from breast; bisphosphonate for **angiogenesis** treatment)
IT Antitumor agents
(mammary gland, metastasis, to lung; bisphosphonate for **angiogenesis** treatment)
IT Lung, **neoplasm**
(metastasis, inhibitors, from breast; bisphosphonate for **angiogenesis** treatment)
IT Mammary gland
(metastasis, inhibitors, to lung; bisphosphonate for **angiogenesis** treatment)
IT Antitumor agents
(metastasis; bisphosphonate for **angiogenesis** treatment)
IT Proliferation inhibition
(proliferation inhibitors; bisphosphonate for **angiogenesis** treatment)
IT Drug delivery systems
(transdermal; bisphosphonate for **angiogenesis** treatment)
IT 132508-02-2, U 81581
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(U 81581; bisphosphonate for **angiogenesis** treatment)
IT 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(bisphosphonate for **angiogenesis** treatment)
IT **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid
13598-36-2D, Phosphonic acid, bisphosphonates **40391-99-9**,
Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8**
66376-36-1, Alendronic acid **79778-41-9**
89987-06-4, Tiludronic acid **105462-24-6**, Risedronic acid
105462-24-6D, Risedronic acid, N-Me pyridinium salts 112855-84-2, FR
78844 **114084-78-5**, Ibandronic acid **118072-93-8**,
Zoledronic acid 118072-93-8D, mixed sodium salts 125946-91-0
125946-92-1, EB 1053 132423-94-0 138844-81-2, BM 21.0955
180064-38-4, YM 529 183490-29-1, **NE 10446**
197313-76-1, **NE 10244**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bisphosphonate for **angiogenesis** treatment)

=>

L10 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:76588 CAPLUS
TITLE: Combinations comprising epothilones and antiproliferative uses thereof
INVENTOR(S): Chen, Tianling; Greeley, Diane; Rothermel, John David; Wartmann, Markus; Wood, Jeanette Marjorie
PATENT ASSIGNEE(S): Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007924	A2	20030130	WO 2002-EP8020	20020718

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR

PRIORITY APPLN. INFO.: US 2001-306559P P 20010719
US 2001-306560P P 20010719
US 2001-306571P P 20010719

AB The invention relates to a combination which comprises (a) a **bisphosphonate**, a platinum compd. or a vasculostatic compd. and (b) an epothilone deriv. of formula (I), wherein A represents O or NRN, wherein RN is hydrogen or lower alkyl, R is hydrogen or lower alkyl, and Z is O or a bond, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier for simultaneous, sep. or sequential use, in particular for the delay of progression or treatment of a proliferative disease, esp. a solid **tumor** disease; a pharmaceutical compn., a com. package or product comprising such a combination; the use of such a combination for the prepn. of a medicament for the delay of progression or treatment of a proliferative disease and to a method of treatment of a warm-blooded animal.

IT INDEXING IN PROGRESS
IT Animal cell line
(DU-145; combinations comprising epothilones and antiproliferative uses thereof)
IT Animal cell line
(PC-3MM2; combinations comprising epothilones and antiproliferative uses thereof)
IT Drug delivery systems
(carriers; combinations comprising epothilones and antiproliferative uses thereof)
IT Uterus, **neoplasm**
(cervix; combinations comprising epothilones and antiproliferative uses thereof)
IT Intestine, **neoplasm**
(colon; combinations comprising epothilones and antiproliferative uses thereof)
IT **Angiogenesis** inhibitors
Antitumor agents
Cytotoxic agents

Drug delivery systems
Human
Lung, **neoplasm**
Ovary, **neoplasm**
(combinations comprising epothilones and antiproliferative uses thereof)

IT Bone, **neoplasm**
(metastasis, of prostate **cancer**; combinations comprising epothilones and antiproliferative uses thereof)

IT Prostate gland
(**neoplasm**, hormone-refractory; combinations comprising epothilones and antiproliferative uses thereof)

IT Head
Neck, anatomical
(**neoplasm**; combinations comprising epothilones and antiproliferative uses thereof)

IT Disease, animal
(proliferative; combinations comprising epothilones and antiproliferative uses thereof)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**bisphosphonate**; combinations comprising epothilones and antiproliferative uses thereof)

IT **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid **40391-99-9**, Pamidronic acid 41575-94-4, Carboplatin 61825-94-3, Oxaliplatin **66376-36-1**, Alendronic acid **89987-06-4**, Tiludronic acid **105462-24-6**, Risedronic acid **114084-78-5**, Ibandronic acid **118072-93-8**, **Zoledronic** acid 152044-54-7D, Epothilone b, derivs. 212142-18-2, ptk787
RL: PAC (Pharmacological activity); PEP (Physical, engineering or chemical process); PYP (Physical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(combinations comprising epothilones and antiproliferative uses thereof)

L10 ANSWER 2 OF 25. CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:44926 CAPLUS
DOCUMENT NUMBER: 138:100267
TITLE: The use of **zoledronic** acid, a novel, highly potent **bisphosphonate**, for the treatment of hypercalcemia of malignancy
AUTHOR(S): Major, Pierre
CORPORATE SOURCE: Department of Medicine, McMaster University, Hamilton, ON, Can.
SOURCE: Oncologist (2002), 7(6), 481-491
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Hypercalcemia of malignancy is a serious complication of **cancer** that affects patients with and without bone metastases. A single infusion of pamidronate disodium, a nitrogen-contg. **bisphosphonate**, effectively normalizes serum calcium in the majority of patients treated for up to 1 mo. **Zoledronic** acid is a new-generation, heterocyclic nitrogen-contg. **bisphosphonate** and the most potent inhibitor of bone resorption identified to date. The natural history, clin. presentation, and treatment of hypercalcemia of malignancy are reviewed, with a focus on the mechanisms of action and relative efficacy and safety of **bisphosphonate** therapies. The

improved efficacy of **zoledronic** acid compared with pamidronate disodium has been demonstrated in a pooled anal. of two randomized clin. trials in patients with hypercalcemia of malignancy. In these trials, both **zoledronic** acid and pamidronate disodium were safe and well tolerated; however, **zoledronic** acid treatment resulted in a significantly higher no. of complete responses, more rapid calcium normalization, and more durable responses compared with pamidronate disodium. Given the superior efficacy and comparable safety profile of **zoledronic** acid compared with pamidronate disodium, **zoledronic** acid is likely to become the treatment of choice for hypercalcemia of malignancy.

IT Bone, **neoplasm**
(metastasis; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT Bone
(resorption, inhibitors; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT Human
Neoplasm
(use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of **zoledronic** acid highly potent **bisphosphonate** for treatment of hypercalcemia of malignancy in **cancer** patients)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:948341 CAPLUS

TITLE: Pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma

AUTHOR(S): Gordon, Sharon; Helfrich, Miep H.; Sati, Hamdi I. A.; Greaves, Michael; Ralston, Stuart H.; Culligan, Dominic J.; Soutar, Richard L.; Rogers, Michael J.

CORPORATE SOURCE: Department of Medicine and Therapeutics, University of Aberdeen Medical School, Aberdeen, UK

SOURCE: British Journal of Haematology (2002), 119(2), 475-483
CODEN: BJHEAL; ISSN: 0007-1048

PUBLISHER: Blackwell Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Anti-resorptive **bisphosphonates**, such as pamidronate, are an effective treatment for osteolytic disease and hypercalcemia in patients with multiple myeloma, but have also been shown to cause apoptosis of myeloma cell lines in vitro. In this study, we found that a single infusion of pamidronate, in 16 newly diagnosed patients with multiple myeloma, caused a marked increase in apoptosis of plasma cells in vivo in 10 patients and a minimal increase in four patients ($P < 0.05$). The nitrogen-contg. **bisphosphonates** pamidronate and

zoledronic acid also induced apoptosis of authentic, human bone marrow-derived plasma cells in vitro. Apoptosis of plasma cells in vitro was probably caused by inhibition of the mevalonate pathway and loss of prenylated small GTPases, as even low concns. (.gtoreq. 1 .mu.mol/l) of **zoledronic** acid caused accumulation of unprenylated Rap1A in cultures of bone marrow mononuclear cells in vitro. GGTI-298, a specific inhibitor of geranylgeranyl transferase I, also induced apoptosis in human plasma cells in vitro, suggesting that geranylgeranylated proteins play a role in signaling pathways that prevent plasma cell death. Our results suggest that pamidronate may have direct and/or indirect anti-**tumor** effects in patients with multiple myeloma, which has important implications for the further development of the more potent nitrogen-contg. **bisphosphonates**, such as **zoledronic** acid, in the treatment of myeloma.

IT Multiple myeloma
(inhibitor; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Antitumor agents
(multiple myeloma; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Apoptosis
Human
Prenylation
Signal transduction, biological
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Lymphocyte
(plasma cell; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Bone marrow
(plasma cells; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT Alkenylation
(tetramethylhexadecatetraenylation; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT 9059-32-9 135371-29-8, Geranylgeranyl transferase I 180977-44-0, GGTI-298
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

IT **40391-99-9** 57248-88-1, Aredia **118072-93-8**, Zometa
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pamidronate causes apoptosis of plasma cells in vivo in patients with multiple myeloma)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:888561 CAPLUS
DOCUMENT NUMBER: 137:363054
TITLE: Combination comprising N-(5-[4-(4-methylpiperazinomethyl)benzoylamino]-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidineamine and a chemotherapeutic agent
INVENTOR(S): Bruns, Christian; Buchdunger, Elisabeth; O'Reilly, Terence; Silberman, Sandra Leta; Wartmann, Markus;

Weckbecker, Gisbert
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092091	A1	20021121	WO 2002-EP5362	20020515

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2001-291427P P 20010516

AB A method of treating a warm-blooded animal, esp. a human, having a proliferative disease or acute or chronic transplant rejection comprises administering to the animal a combination contg. comprises (a) N-(5-[4-(4-methylpiperazinomethyl)benzoylamino]-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidineamine (imatinib) and (b) a chemotherapeutic agent selected from antineoplastic agents, esp. as defined herein, and agents effective in treating acute or chronic transplant rejection; a combination comprising (a) and (b) as defined above and optionally at least 1 carrier for simultaneous, sep. or sequential use, in particular for the delay of progression or treatment of a proliferative disease, esp. a solid **tumor** disease. That STI 571 (mesylate of imatinib) induces synergistic therapeutic interactions with Taxol in rat glioma **tumor** xenografts in female mice.

IT Androgens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiandrogens; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Estrogens
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiestrogens; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Prostate gland
(carcinoma; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Alkylating agents, biological
Antitumor agents
Human
Microtubule
(combination comprising imatinib and chemotherapeutic antitumor agent)

IT Bone, **neoplasm**
(metastasis; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Drug interactions
(synergistic; combination comprising imatinib and chemotherapeutic antitumor agent)

IT Transplant and Transplantation
(treatment of rejection of; combination comprising imatinib and chemotherapeutic antitumor agent)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; combination comprising imatinib and chemotherapeutic antitumor agent)
IT 33515-09-2, Gonadorelin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combination comprising imatinib and chemotherapeutic antitumor agent)
IT 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 112809-51-5, Letrozole 114977-28-5, Docetaxel **118072-93-8**, **Zoledronic** acid 152459-95-5, Imatinib 180288-69-1, Trastuzumab 220127-57-1, STI 571
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination comprising imatinib and chemotherapeutic antitumor agent)
IT 9039-48-9, Aromatase 142805-56-9, Topoisomerase II 143180-75-0 372092-80-3, Protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combination comprising imatinib and chemotherapeutic antitumor agent)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:884654 CAPLUS
DOCUMENT NUMBER: 137:362484
TITLE: Pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases
AUTHOR(S): Chen, Tianling; Berenson, James; Vescio, Robert; Swift, Regina; Gilchick, Alicia; Goodin, Susan; LoRusso, Patricia; Ma, Peiming; Ravera, Christina; Deckert, Fabienne; Schran, Horst; Seaman, John; Skerjanec, Andrej
CORPORATE SOURCE: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
SOURCE: Journal of Clinical Pharmacology (2002), 42(11), 1228-1236
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The pharmacokinetics, pharmacodynamics, and safety of **zoledronic** acid (Zometa), a new-generation **bisphosphonate**, were evaluated in 36 patients with **cancer** and bone metastases. **Zoledronic** acid (by specific RIA) and markers of bone turnover were detd. in plasma and urine after three consecutive infusions (qx28 days) of 4 mg/5 min (n = 5), 4 mg/15 min (n = 7), 8 mg/15 min (n = 12), or 16 mg/15 min (n = 12). **Zoledronic** plasma disposition was multiphasic, with half-lives of 0.2 and 1.4 h representing an early, rapid decline of concns. from the end-of-infusion Cmax to < 1% of Cmax at 24 h postdose and half-lives of 39 and 4526 h describing subsequent phases of very low concns. between days 2 and 28 postdose. AUC0-24 h and Cmax were dose proportional and showed little accumulation (AUC0.24 h ratio between the third and first dose was 1.28). Prolonging the infusion from 5 to 15 min lowered Cmax by 34%, with no effect on AUC0-24 h. Urinary excretion of **zoledronic** acid was independent of in fusion duration, dose, or no. of doses, showing av. Ae0-24 h of 38% .+-. 13%, 41% .+-. 14%, and 37% .+-. 17%, resp., after 4, 8, and 16 mg. Only trace amts. of drug were detectable in post 24-h urines. Renal clearance (Ae0-24 h)/(AUC0-24 h) was on av. 69.+-.28, 81.+-.40, and 54.+-.34 mL/min after 4, 8, and 16 mg, resp., and showed a moderate correlation (r = 0.5; p < 0.001) with creatinine clearance, which was 84.+-.23, 82.+-.25, and 80.+-.40 mL/min

for the dose groups at baseline. Adverse events and changes from baseline in vital signs and clin. lab. variables showed no relationship in terms of type, frequency, or severity with **zoledronic** acid dose or pharmacokinetic parameters. **Zoledronic** acid produced significant declines from baseline in serum and/or creatinine-cor. urine C-telopeptide (by 74%), N-telopeptide (69%), pyridinium cross-links (19-33%), and calcium (62%), with an increasing trend (by 12%) in bone alk. phosphatase. There was no relationship of the magnitude and duration of these changes with **zoledronic** acid dose, Ae0-24 h, AUC0-24 h, or Cmax. The antiresorptive effects were evident within 1 day postdose and were maintained over 28 days across all dose levels, supporting monthly dosing with 4 mg **zoledronic** acid.

IT Bone, **neoplasm**
(metastasis; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Human
Neoplasm
(pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Bone
(resorption, inhibitors; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT Bone
(resorption; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

IT **118072-93-8**, Zometa
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics and pharmacodynamics of **zoledronic** acid in **cancer** patients with bone metastases)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:866298 CAPLUS
DOCUMENT NUMBER: 137:320061
TITLE: **Zoledronic** acid reduces skeletal-related events in patients with osteolytic metastases: A double-blind, randomized dose-response study. [Erratum to document cited in CA135:189951]
AUTHOR(S): Berenson, James R.; Rosen, Lee S.; Howell, Anthony; Porter, Lester; Coleman, Robert E.; Morley, Walter; Dreicer, Robert; Kuross, Steven A.; Lipton, Allan; Seaman, John J.
CORPORATE SOURCE: Cedars-Sinai Medical Center, Los Angeles, CA, USA
SOURCE: Cancer (New York, NY, United States) (2001), 91(10), 1956
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cor. address for reprints is: James R. Berenson, M.D., Cedars-Sinai Medical Center, Bev. Mod. 1, Room 100, 8700 Beverly Boulevard, Los

Angeles, CA 90048; Fax: (310)423-1977; E-mail: berensonj@cshs.org.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

IT Human
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

IT **118072-93-8, Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases (Erratum))

L10 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:849414 CAPLUS
DOCUMENT NUMBER: 137:346153
TITLE: Pharmaceutical uses of **bisphosphonates**
INVENTOR(S): Seaman, John J.
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087555	A2	20021107	WO 2002-EP4771	20020430
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				

PRIORITY APPLN. INFO.: US 2001-288220P P 20010502
OTHER SOURCE(S): MARPAT 137:346153

AB A method for the treatment of prostate **cancers** and other **cancers** having assocd. osteoblastic (osteosclerotic) metastases in a patient in need of such treatment comprising administering an effective amt. of an N-**bisphosphonate**, esp. **zoledronic** acid or a salt or any hydrate thereof, to the patient. **Bisphosphonates** are formulated into various delivery systems, such as capsules, adhesive transdermal system, and injections. For example, **zoledronic** acid 4 mg, given as a 15-min infusion, was well tolerated. **Zoledronic** acid 4 mg 15-min infusions every 3 wk significantly reduce skeletal-related events in patients with metastatic prostate **cancer** refractory to hormonal therapy.

IT Antitumor agents
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Human
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases in humans)

IT Drug delivery systems
(capsules; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Drug delivery systems

(injections; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Bone, **neoplasm**
(metastasis; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Prostate gland
(**neoplasm**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT Drug delivery systems
(transdermal; compns. contg. **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 197313-76-1, **NE 10244**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10244**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 183490-29-1, **NE 10446**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10446**; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 132508-02-2, U 81581
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(U 81581; **bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **40391-99-9**, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8** **66376-36-1**, Alendronic acid **79778-41-9**, 6-Amino-1-hydroxyhexane-1,1-diphosphonic acid **105462-24-6**, Risedronic acid 112855-84-2, FR 78844 **114084-78-5**, Ibandronic acid **118072-93-8**, **Zoledronic** acid **125946-92-1**, EB 1053 131654-46-1 132423-94-0 **180064-38-4**, YM 529
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** for treatment of prostate other **cancers** assocd. with osteoblastic metastases)

L10 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:842416 CAPLUS
DOCUMENT NUMBER: 137:320059
TITLE: A randomized, placebo-controlled trial of **zoledronic** acid in patients with hormone-refractory metastatic prostate carcinoma
AUTHOR(S): Saad, Fred; Gleason, Donald M.; Murray, Robin; Tchekmedyian, Simon; Venner, Peter; Lacombe, Louis; Chin, Joseph L.; Vinholes, Jeferson J.; Goas, J. Allen; Chen, Bee
CORPORATE SOURCE: Zoledronic Acid Prostate Cancer Study Group, Hopital Notre-Dame, Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Can.
SOURCE: Journal of the National Cancer Institute (2002), 94(19), 1458-1468
CODEN: JNCIEQ; ISSN: 0027-8874
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone metastases are a common cause of morbidity in patients with prostate carcinoma. We studied the effect of a new **bisphosphonate**, **zoledronic** acid, which blocks bone destruction, on skeletal

complications in prostate **cancer** patients with bone metastases. Patients with hormone-refractory prostate **cancer** and a history of bone metastases were randomly assigned to a double-blind treatment regimen of i.v. **zoledronic** acid at 4 mg (N = 214), **zoledronic** acid at 8 mg (subsequently reduced to 4 mg; 8/4) (N = 221), or placebo (N = 208) every 3 wk for 15 mo. Proportions of patients with skeletal-related events, time to the first skeletal-related event, skeletal morbidity rate, pain and analgesic scores, disease progression, and safety were assessed. All statistical tests were two-sided. Approx. 38% of patients who received **zoledronic** acid at 4 mg, 28% who received **zoledronic** acid at 8/4 mg, and 31 % who received placebo completed the study. A greater proportion of patients who received placebo had skeletal-related events than those who received **zoledronic** acid at 4 mg (44.2 % vs. 33.2 %; difference = -11.0 %, 95% confidence interval [CI] = -20.3% to -1.8%; P = .021) or those who received **zoledronic** acid at 8/4 mg (38.5%; difference vs. placebo = -5.8%, 95% CI = -15.1% to 3.6%; P = .222). Median time to first skeletal-related event was 321 days for patients who received placebo, was not reached for patients who received **zoledronic** acid at 4 mg (P = .011 vs. placebo), and was 363 days for those who received **zoledronic** acid at 8/4 mg (P = .491 vs. placebo). Compared with urinary markers in patients who received placebo, urinary markers of bone resorption were statistically significantly decreased in patients who received **zoledronic** acid at either dose (P = .001). Pain and analgesic scores increased more in patients who received placebo than in patients who received **zoledronic** acid, but there were no differences in disease progression, performance status, or quality-of-life scores among the groups. **Zoledronic** acid at 4 mg given as a 15-min infusion was well tolerated, but the 8-mg dose was assocd. with renal function deterioration. **Zoledronic** acid at 4 mg reduced skeletal-related events in prostate **cancer** patients with bone metastases.

IT Prostate gland
(carcinoma, metastasis; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT Bone, **neoplasm**
(metastasis; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT Antitumor agents
Human
(new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

IT **118072-93-8**, Zometa
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new **bisphosphonate, zoledronic** acid, in patients with hormone-refractory metastatic prostate carcinoma)

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:793432 CAPLUS
DOCUMENT NUMBER: 137:304812
TITLE: A drug for use in bone grafting
INVENTOR(S): Little, David Graham

PATENT ASSIGNEE(S): The Royal Alexandra Hospital for Children, Australia
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080933	A1	20021017	WO 2002-AU412	20020328

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: AU 2001-4187 A 20010403
AU 2001-9613 A 20011217

AB A drug and method for bone grafting which improves the osteoinductive and/or osteoconductive potential of a bone graft, bone graft substitute or extenders. The drug is selected from the group consisting of **bisphosphonates** which may be administered to a subject either prior to, during or after a bone grafting procedure.

IT Bone morphogenetic proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(7; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-2; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-4; drug for use in bone grafting)
IT Proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BMP-6; drug for use in bone grafting)
IT Transplant and Transplantation
(allotransplant; drug for use in bone grafting)
IT Spinal column
(arthrodesis; drug for use in bone grafting)
IT Joint, anatomical
(arthroplasty; drug for use in bone grafting)
IT Bone
(artificial; drug for use in bone grafting)
IT Infection
(bone loss due to; drug for use in bone grafting)
IT Transplant and Transplantation
(bone, substitutes or extenders; drug for use in bone grafting)
IT Transplant and Transplantation
(bone; drug for use in bone grafting)
IT Drug delivery systems
(carriers; drug for use in bone grafting)
IT Osteoarthritis
(congenital pseudo-; drug for use in bone grafting)
IT Bone, disease
(delayed union or non-union of a bone; drug for use in bone grafting)
IT Bone
(demineralization; drug for use in bone grafting)
IT Metabolism, animal

(disorder; drug for use in bone grafting)
IT Bone marrow
Cement
Cyst, pathological
Human
Human
Hyperparathyroidism
Neoplasm
Osteomyelitis
Putty
Skull
Sponges (artificial)
Surgery
(drug for use in bone grafting)
IT Collagens, biological studies
Gelatins, biological studies
Osteocalcins
Polymers, biological studies
Resins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
IT Kidney, disease
(failure; drug for use in bone grafting)
IT Bone, disease
(fracture, open; drug for use in bone grafting)
IT Bone, disease
(fracture; drug for use in bone grafting)
IT Drug delivery systems
(gels; drug for use in bone grafting)
IT Drug delivery systems
(implants; drug for use in bone grafting)
IT Drug delivery systems
(injections, i.m.; drug for use in bone grafting)
IT Drug delivery systems
(injections, i.v.; drug for use in bone grafting)
IT Jaw
(mandibula; drug for use in bone grafting)
IT Jaw
(maxilla; drug for use in bone grafting)
IT Medical goods
(meshes; drug for use in bone grafting)
IT Bone
(minerals; drug for use in bone grafting)
IT Drug delivery systems
(oral; drug for use in bone grafting)
IT Surgery
(orthopedic; drug for use in bone grafting)
IT Bone, disease
(osteolysis; drug for use in bone grafting)
IT Drug delivery systems
(parenterals; drug for use in bone grafting)
IT Drug delivery systems
(s.c.; drug for use in bone grafting)
IT Medical goods
(sheets, flexible; drug for use in bone grafting)
IT Drug delivery systems
(solns., injection; drug for use in bone grafting)
IT Bone
(tibia; drug for use in bone grafting)
IT Drug delivery systems
(transdermal; drug for use in bone grafting)
IT Bone

(transplant, substitutes or extenders; drug for use in bone grafting)
IT Bone
(transplant; drug for use in bone grafting)
IT Injury
(trauma; drug for use in bone grafting)
IT Transplant and Transplantation
(xenotransplant; drug for use in bone grafting)
IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-; drug for use in bone grafting)
IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; drug for use in bone grafting)
IT **2809-21-4 10596-23-3 40391-99-9**
66376-36-1, Alendronate **79778-41-9**, Neridronate
89987-06-4, Tiludronate **105462-24-6 114084-78-5**
, Ibandronate **118072-93-8**, **Zoledronic** acid
121368-58-9, Olpadronate **125946-92-1**, EB-1053 138330-18-4,
Incadronate **180064-38-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
IT 56-81-5, Glycerol, biological studies 7440-70-2D, Calcium, compds.
7778-18-9, Osteoset 26009-03-0, Polyglycolic acid 26023-30-3,
Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] 26100-51-6, Polylactic acid
26124-68-5, Polyglycolic acid 61912-98-9, Insulinlike growth factor
62031-54-3, Fibroblast growth factor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug for use in bone grafting)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:780471 CAPLUS
DOCUMENT NUMBER: 137:288664
TITLE: **Zoledronic** acid is effective in the treatment of prostate **cancer** patients with bone metastases
AUTHOR(S): Maung, Kavita; Higano, Celestia
CORPORATE SOURCE: USA
SOURCE: Clinical Prostate Cancer (2002), 1(1), 12-13
CODEN: CPCLC4; ISSN: 1540-0352
PUBLISHER: Cancer Information Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study included adult patients with prostate **cancer** and bone metastases, an Eastern Cooperative Oncol. Group performance status (PS) of .ltoreq.2, and serum creatinine levels of .ltoreq.3 mg/dL. Patients were required to have rising prostate-specific antigen levels and base-line serum testosterone < 50 mg/dL. Patients were randomized to treatment with either **zoledronic** acid 4 mg or 8 mg or placebo to be given 5-min infusion every 3 wk. There was a statistically significant redn. in SREs (skeletal-related events) seen in the **zoledronic** acid arm. Thirty-three percent of patients on the **zoledronic** acid arm experienced SREs - compared to 44% of patients on the placebo arm (P = 0.021). Patients receiving 4 mg of **zoledronic** acid showed significantly reduced frequency of SREs and increased time to first SRE compared to patients on placebo. The overall median survival was not significantly increased in patients treated with **zoledronic** acid compared to placebo. Based on these promising results, the US FDA has recently approved **zoledronic** acid for the treatment of bone

metastases in patients who have failed initial hormonal therapy for prostate **cancer**.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Prostate gland
(**neoplasm**, metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Antitumor agents
(prostate **cancer** bone metastasis; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT Human
(**zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; **zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid is effective in treatment of prostate **cancer** patients with bone metastases)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:651461 CAPLUS
DOCUMENT NUMBER: 137:194877
TITLE: Novel approaches to the management of bone metastases in patients with breast **cancer**
AUTHOR(S): Hortobagyi, Gabriel N.
CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Seminars in Oncology (2002), 29(3, Suppl. 11), 134-144
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Bone metastases appear frequently in patients with advanced breast **cancer**. They are assocd. with substantial morbidity and occasionally produce life-threatening complications. Systemic anticancer therapies (chemotherapy and hormonal therapies) represent the treatment of choice for these and other distant metastases from breast **cancer**. Aggressive use of prophylactic and therapeutic orthopedic surgery is warranted, esp. for lesions in wt.-bearing areas. Judicious use of external radiotherapy and bone-seeking radionuclides contributes to the control of pain and local control of lesions in strategic locations. In recent years, the development of osteoclast-inhibitory therapy added a new dimension to symptom control and prevention of skeletal complications. The **bisphosphonates**, clodronate, pamidronate, and **zoledronic** acid, are potent osteoclast inhibitors with marked clin. effects. They represent the drugs of choice for control of hypercalcemia of malignancy, and they are crit. adjuvants to systemic anticancer therapy of metastatic disease. More recently, the development of recombinant osteoprotegerin and an anti-parathyroid hormone-related protein monoclonal antibody represent promising new options for the treatment of patients with bone metastases.

IT Antitumor agents
(breast **cancer** bone metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Bone, **neoplasm**
(metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Mammary gland
(**neoplasm**, metastasis; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Human
Radiotherapy
(novel approaches to management of bone metastases in patients with breast **cancer**)
IT Surgery
(orthopedic; novel approaches to management of bone metastases in patients with breast **cancer**)
IT Bone
(resorption inhibitor; novel approaches to management of bone metastases in patients with breast **cancer**)
IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Bisphosphonate**; novel approaches to management of bone metastases in patients with breast **cancer**)
IT **10596-23-3 40391-99-9 118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel approaches to management of bone metastases in patients with breast **cancer**)
REFERENCE COUNT: 92 THERE ARE 92 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:539062 CAPLUS
DOCUMENT NUMBER: 137:226194
TITLE: Highly Potent Geminal **Bisphosphonates**. From Pamidronate Disodium (Aredia) to **Zoledronic** Acid (Zometa)
AUTHOR(S): Widler, Leo; Jaeggi, Knut A.; Glatt, Markus; Mueller, Klaus; Bachmann, Rolf; Bisping, Michael; Born, Anne-Ruth; Cortesi, Reto; Guiglia, Gabriela; Jeker, Heidi; Klein, Remy; Ramseier, Ueli; Schmid, Johann; Schreiber, Gerard; Seltenmeyer, Yves; Green, Jonathan R.
CORPORATE SOURCE: Arthritis and Bone Metabolism Therapeutic Area, Novartis Pharma Research, Basel, CH-4002, Switz.
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3721-3738
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** (BPs) are pyrophosphate analogs in which the oxygen in P-O-P has been replaced by a carbon, resulting in a metabolically stable P-C-P structure. Pamidronate (1b, Novartis), a second-generation BP, was the starting point for extensive SAR studies. Small changes of the structure of pamidronate lead to marked improvements of the inhibition of osteoclastic resorption potency. Alendronate (1c, MSD), with an extra methylene group in the N-alkyl chain, and olpadronate

(1h, Gador), the N,N-di-Me analog, are about 10 times more potent than pamidronate. Extending one of the N-Me groups of olpadronate to a pentyl substituent leads to ibandronate (1k, Roche, Boehringer-Mannheim), which is the most potent close analog of pamidronate. Even slightly better antiresorptive potency is achieved with derivs. having a Ph group linked via a short aliph. tether of three to four atoms to nitrogen, the second substituent being preferentially a Me group (e.g., 4g, 4j, 5d, or 5r). The most potent BPs are found in the series contg. a heteroarom. moiety (with at least one nitrogen atom), which is linked via a single methylene group to the geminal **bisphosphonate** unit. **Zoledronic** acid (6i), the most potent deriv., has an ED50 of 0.07 mg/kg in the TPTX in vivo assay after s.c. administration. It not only shows by far the highest therapeutic ratio when comparing resorption inhibition with undesired inhibition of bone mineralization but also exhibits superior renal tolerability. **Zoledronic** acid (6i) has thus been selected for clin. development under the registered trade name Zometa. The results of the clin. trials indicate that low doses are both efficacious and safe for the treatment of **tumor**-induced hypercalcemia, Paget's disease of bone, osteolytic metastases, and postmenopausal osteoporosis.

IT Methyl group
Phenyl group
Structure-activity relationship
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Osteoclast
(bone resorption; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Bone
(resorption, osteoclastic; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT Osteoporosis
(therapeutic agents, postmenopausal; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 29712-30-9P 32545-72-5P 56152-35-3P 63132-38-7P 63132-40-1P
63161-30-8P **66376-36-1P**, Alendronate 67242-32-4P
79778-41-9P, Neridronate 86235-67-8P 89732-96-7P
104261-68-9P **114084-78-5P**, Ibandronate 114084-82-1P
114119-81-2P 116162-22-2P 116786-78-8P 116786-79-9P 116786-83-5P
116786-85-7P 116786-88-0P 116786-89-1P 116786-90-4P 118054-12-9P
118054-15-2P 118054-16-3P 118054-18-5P 118054-19-6P 118054-20-9P
118054-23-2P 118054-31-2P 118054-32-3P 118054-33-4P 118054-41-4P
118054-42-5P 118054-51-6P 118054-52-7P **118072-93-8P**
118694-16-9P 121368-58-9P, Olpadronate **124351-85-5P**
124369-71-7P 124369-72-8P 124369-73-9P 124369-77-3P 124369-80-8P
124369-81-9P 124369-83-1P 125946-91-0P 128202-57-3P 129951-00-4P
129951-01-5P 129951-02-6P 131654-39-2P 131654-40-5P 131654-41-6P
131654-58-5P 132423-84-8P 132423-86-0P 132423-87-1P 132423-88-2P
132423-89-3P 132423-90-6P 132423-92-8P 132423-94-0P 132423-95-1P
132423-96-2P 132423-97-3P 132423-98-4P 132423-99-5P 132424-00-1P
132424-01-2P 134579-54-7P 134579-55-8P 134579-56-9P 136671-90-4P
142830-99-7P 149226-80-2P 154188-60-0P 183446-90-4P 183446-98-2P
209002-31-3P 209002-32-4P 459870-45-2P 459870-46-3P 459870-47-4P
459870-48-5P 459870-49-6P 459870-50-9P 459870-51-0P 459870-52-1P
459870-53-2P 459870-54-3P 459870-55-4P 459870-56-5P 459870-57-6P
459870-58-7P 459870-59-8P 459870-60-1P 459870-61-2P
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT **40391-99-9** 41003-10-5
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological

activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 96-50-4, 2-Aminothiazole 936-44-7, 3-Phenylpyrrolidine 1008-73-7 1660-94-2, Tetraethyl methylenebisphosphonate 3612-20-2, 1-Benzylpiperidin-4-one 4584-46-7, 2-Chloroethyldimethylamine hydrochloride 6646-51-1, 2-Amino-1-methylimidazole 7305-71-7, 2-Amino-5-methylthiazole 7552-07-0, 1,2,4-Thiadiazol-5-amine 16270-07-8 21722-08-7 22944-67-8 41441-40-1 149692-49-9 459870-63-4 459870-64-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 2302-39-8P, 4,5-Dimethylimidazole 17334-08-6P 120418-62-4P 183446-91-5P 183446-95-9P 459870-65-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**bisphosphonates** prepn. and structure-related bone antiresorptive properties)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; **bisphosphonates** prepn. and structure-related bone antiresorptive properties)

REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:526926 CAPLUS
DOCUMENT NUMBER: 138:100192
TITLE: Pharmacologic profile of **zoledronic** acid: A highly potent inhibitor of bone resorption
AUTHOR(S): Green, Jonathan R.; Rogers, Michael J.
CORPORATE SOURCE: Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Drug Development Research (2002), 55(4), 210-224
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Bisphosphonates** are effective in treating benign and malignant skeletal diseases characterized by enhanced osteoclastic bone resorption (i.e., osteoporosis, Paget's disease, **tumor**-induced osteolysis). The nitrogen-contg. **bisphosphonate** pamidronate is currently the std. treatment for hypercalcemia of malignancy (HCM) and skeletal complications of bone metastases. **Zoledronic** acid, a novel nitrogen-contg. **bisphosphonate** with an imidazole substituent, has demonstrated more potent inhibition of osteoclast-mediated bone resorption than all other **bisphosphonates**, including pamidronate, in both in vitro and in vivo preclin. models. **Zoledronic** acid inhibited ovariectomy-induced bone loss in adult monkeys and rats, and long-term treatment prevented skeletal turnover and subsequent bone loss, reduced cortical porosity, and increased mech. strength. **Zoledronic** acid also significantly inhibited bone loss assocd. with **arthritis**, bone metastases, and prosthesis loosening. The increased potency of **zoledronic** acid vs. pamidronate has been demonstrated clin.: **zoledronic** acid (4 or 8 mg iv) was superior to pamidronate (90 mg iv) in normalizing cor. serum calcium in patients with HCM. In patients with bone metastases, low doses of **zoledronic** acid (.ltoreq. 2 mg) suppressed bone resorption markers .ltoreq. 50% below baseline, whereas pamidronate 90 mg yielded only 20 to 30% suppression. Importantly, the increased potency of **zoledronic** acid is not assocd. with an increased incidence of local (bone) or systemic adverse events. **Zoledronic** acid does

not impair bone mineralization and, compared with pamidronate, has a greater renal and intestinal tolerability therapeutic index. Thus, based on preclin. assays and clin. data, **zoledronic** acid is the most potent **bisphosphonate** tested to date. Given its potency and excellent safety profile, **zoledronic** acid is now poised to become the new std. of treatment for HCM and metastatic bone disease.

IT Human
(bone resorption inhibitor, **zoledronic** acid)

IT Bone, **neoplasm**
(metastasis; bone resorption inhibitor, **zoledronic** acid)

IT Bone
(resorption, inhibitors; bone resorption inhibitor, **zoledronic** acid)

IT 13598-36-2D, Phosphonic acid, alkylidinebis- derivs.
RL: PAC (Pharmacological activity); BIOL (Biological study)
(bone resorption inhibitor, **zoledronic** acid)

IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bone resorption inhibitor, **zoledronic** acid)

IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hypercalcemia; bone resorption inhibitor, **zoledronic** acid)

REFERENCE COUNT: 105 THERE ARE 105 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:486034 CAPLUS
DOCUMENT NUMBER: 138:66277
TITLE: The **bisphosphonate zoledronic** acid impairs membrane localization and induces cytochrome c release in breast **cancer** cells
AUTHOR(S): Senaratne, S. G.; Mansi, J. L.; Colston, K. W.
CORPORATE SOURCE: Department of Oncology, Gastroenterology, Endocrinology and Metabolism, St. George's Hospital Medical School, London, SW17 0RE, UK
SOURCE: British Journal of Cancer (2002), 86(9), 1479-1486
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Forced expression of the antiapoptotic protein bcl-2 attenuated **zoledronic** acid-induced loss of cell viability and induction of DNA fragmentation in human breast **cancer** MDA-MB-231 cells. **Zoledronic** acid-mediated apoptosis was assocd. with a time- and concn.-related release of mitochondrial cytochrome c into the cytosol in two cell lines. Rescue of the cells by preincubation with a caspase-3-selective inhibitor and demonstration of procaspase-3 cleavage products by immunoblotting suggested that at least one of the caspases activated in response to **zoledronic** acid treatment is caspase-3. In both MDA-MB-231 and MCF-7 breast **cancer** cells, **zoledronic** acid impaired membrane localization of Ras, indicating reduced prenylation of this protein. These observations demonstrate that **zoledronic** acid-mediated apoptosis is assocd. with cytochrome c release and consequent caspase activation. This process may be initiated by inhibition of the enzymes in the mevalonate pathway, leading to impaired prenylation of key intracellular proteins, including Ras.

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Bcl-2; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release

in human breast **cancer** cells in relation to expression of)

IT Cell membrane
Human
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Ras proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Apoptosis
Signal transduction, biological
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells in relation to)

IT Antitumor agents
(breast **cancer**; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT Mammary gland
(**neoplasm**, inhibitors; **bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT 9007-43-6, Cytochrome c, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT **118072-93-8**, **Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

IT 169592-56-7, Caspase-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells in relation to)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; **zoledronic** acid impairment of membrane localization of Ras and induction of cytochrome c release in human breast **cancer** cells)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:429803 CAPLUS
DOCUMENT NUMBER: 137:41697
TITLE: **Zoledronic** acid versus pamidronate as palliative therapy in **cancer** patients: A Canadian time and motion analysis
AUTHOR(S): Dranitsaris, George; Castel, Liana D.; Baladi, Jean Francois; Schulman, Kevin A.
CORPORATE SOURCE: Department of Molecular Biology, Ontario Cancer Institute and Princess Margaret Hospital, Toronto, ON, M5G 2M9, Can.
SOURCE: Journal of Oncology Pharmacy Practice (2001), 7(1),

27-33
CODEN: JOPPFI; ISSN: 1078-1552
PUBLISHER: Arnold, Hodder Headline
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Pamidronate was an important advance in the palliative treatment of patients with **cancer**. However, pamidronate must be infused over at least 2 h in most patients. **Zoledronic** acid represents the next-generation **bisphosphonate** with a potential for improved efficacy in the palliative care setting. One important advantage of **zoledronic** acid is that it can be administered over a 15-min infusion. To measure the overall efficiency of **zoledronic** acid as compared with pamidronate in the outpatient setting, a USA microcosting model was adapted to Canadian inputs. Time and motion data were collected from six patients being treated with **zoledronic** acid or pamidronate in three USA outpatient **cancer** clinics. Resource use and time impact on outpatient clin. staff were reanalyzed using Canadian cost ests. This included the evaluation of fixed, variable, and labor costs obtained from Canadian sources. The manufacturer provided drug costs. The base case anal. assumed a 5300-ft2 out-patient chemotherapy clinic with eight infusion chairs designated for **bisphosphonate** administration in the province of Ontario. Mean treatment times in the original USA data collected were 2 h, 52 min for pamidronate, and 1 h, 6 min for **zoledronic** acid (a difference of 1 h, 46 min). In the Canadian version of the microcosting model, the overall treatment cost was Can$673 for pamidronate and Can$682 for **zoledronic** acid (2001 Canadian dollars). Findings suggest that the shorter **zoledronic** acid infusion time would allow an addnl. 27 **bisphosphonate** patients to be treated per day. Alternatively, approx. one addnl. hour of chair time could be made available with each zoledonic acid infusion. Sensitivity analyses revealed that (a) the base case results were consistent when geog. region was varied, and (b) the shorter the infusion time for **zoledronic** acid relative to pamidronate, the lesser the cost difference and more patients could be treated daily. In conclusion, **zoledronic** acid may enhance the overall efficiency of outpatient chemotherapy clinics by reducing patient waiting time for **bisphosphonate** administration. These benefits would be obtained at an incremental cost of Can$9 per infusion.
IT Bone, disease
(fracture; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)
IT **Neoplasm**
(humoral hypercalcemia of malignancy; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)
IT Bone, **neoplasm**
(metastasis, pain; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)
IT **Neoplasm**
Simulation and Modeling, biological
(**zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)
IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; **zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)
IT **40391-99-9 118072-93-8, Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid vs. pamidronate as palliative therapy in **cancer** patients)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:428720 CAPLUS
DOCUMENT NUMBER: 137:746
TITLE: Use of **bisphosphonates** for pain treatment
INVENTOR(S): Fox, Alyson; Green, Jonathan; O'Reilly, Terence; Urban, Laszlo; Walker, Katharine
PATENT ASSIGNEE(S): Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002043738	A2	20020606	WO 2001-EP13836	20011127
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
AU 2002017061	A5	20020611	AU 2002-17061	20011127

PRIORITY APPLN. INFO.: GB 2000-29111 A 20001129
WO 2001-EP13836 W 20011127

OTHER SOURCE(S): MARPAT 137:746

AB A method for the treatment of pain, in particular antinociceptive or anti-allodynic treatment of pain, in a patient in need of such treatment, e.g. a patient with osteoporosis or osteopenia, a **tumor** patient, or a patient suffering from an **inflammatory** disease, comprises administering an effective amt. of a **bisphosphonate**, e.g. **zoledronic** acid or salts or hydrates thereof, to the patient.

IT Pain
Skin, disease
(allodynia; **bisphosphonates** for pain treatment)
IT Analgesics
(**bisphosphonates** for pain treatment)
IT Drug delivery systems
(capsules; **bisphosphonates** for pain treatment)
IT Mammary gland
(carcinoma, MRMZ-1 cells, bone pain assoc. with; **bisphosphonates** for pain treatment)
IT **Inflammation**
(**inflammatory** pain; **bisphosphonates** for pain treatment)
IT Drug delivery systems
(infusions, i.v.; **bisphosphonates** for pain treatment)
IT **Neoplasm**
(metastasis, pain assocd. with; **bisphosphonates** for pain treatment)
IT Nerve, disease
(neuropathy, neuropathic pain; **bisphosphonates** for pain treatment)
IT **Neoplasm**
Osteoarthritis

Osteoporosis
Rheumatoid **arthritis**
(pain assocd. with; **bisphosphonates** for pain treatment)
IT Bone
(pain; **bisphosphonates** for pain treatment)
IT Drug delivery systems
(transdermal; **bisphosphonates** for pain treatment)
IT 197313-76-1, **NE 10244**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10244**; **bisphosphonates** for pain treatment)
IT 183490-29-1, **NE 10446**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NE 10446**; **bisphosphonates** for pain treatment)
IT 930-73-4 **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid 13598-36-2D, Phosphonic acid, alkylidenebis- derivs. **40391-99-9**, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8 66376-36-1**, Alendronic acid **79778-41-9 89987-06-4**, Tiludronic acid **105462-24-6**, Risedronic acid 105462-24-6D, Risedronic acid, N-methylpyridinium salts 112855-84-2 **114084-78-5** 118054-32-3 **118072-93-8**, **Zoledronic** acid 125946-91-0 **125946-92-1**, EB 1053 132423-94-0 132508-02-2 138844-81-2, BM 21.0955 **180064-38-4** 433685-76-8
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonates** for pain treatment)

L10 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:868193 CAPLUS
DOCUMENT NUMBER: 136:11141
TITLE: Intravenous administration of a **bisphosphonate**
INVENTOR(S): Seaman, John J.; Sigg, Juergen; Schran, Horst
PATENT ASSIGNEE(S): Novartis A.-G., Switz.
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001089494	A2	20011129	WO 2001-US14886	20010509
WO 2001089494	A3	20020523		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-12209 A 20000519
AB A method of i.v. administering a **bisphosphonate** to a patient in need of **bisphosphonate** treatment comprising i.v. administering 4 mg of **zoledronic** acid or a pharmaceutically acceptable salt thereof over a period of 15 min to a patient in need of said treatment.

IT Antitumor agents
(bone, metastasis; i.v. administration of a **bisphosphonate**)
IT **Neoplasm**
(humoral hypercalcemia of malignancy; i.v. administration of a **bisphosphonate**)
IT Bone, **neoplasm**
(metastasis, inhibitors; i.v. administration of a **bisphosphonate**)
IT Drug delivery systems
(solns., i.v.; i.v. administration of a **bisphosphonate**)
IT 7440-70-2, Calcium, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hypercalcemia; i.v. administration of a **bisphosphonate**)
IT 17341-25-2, Sodium ion, biological studies
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. administration of a **bisphosphonate**)
IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. administration of a **bisphosphonate**)

L10 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:829626 CAPLUS
DOCUMENT NUMBER: 137:57065
TITLE: Early detection of bone metastases in a murine model using fluorescent human breast **cancer** cells: application to the use of the **bisphosphonate zoledronic** acid in the treatment of osteolytic lesions
AUTHOR(S): Peyruchaud, Olivier; Winding, Bent; Pecheur, Isabelle; Serre, Claire-Marie; Delmas, Pierre; Clezardin, Philippe
CORPORATE SOURCE: INSERM Research Unit 403, Faculte de Medecine Laennec, Lyon, Fr.
SOURCE: Journal of Bone and Mineral Research (2001), 16(11), 2027-2034
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: American Society for Bone and Mineral Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A very common metastatic site for human breast **cancer** is bone. The traditional bone metastasis model requires human MDA-MB-231 breast carcinoma cell inoculation into the left heart ventricle of nude mice. MDA-MB-231 cells usually develop osteolytic lesions 3-4 wk after intracardiac inoculation in these animals. Here, the authors report a new approach to study the formation of bone metastasis in animals using breast carcinoma cells expressing the bioluminescent jellyfish protein (green fluorescent protein [GFP]). The authors first established a subclone of MDA-MB-231 cells by repeated in vivo passages in bone using the heart injection model. On stable transfection of this subclone with an expression vector for GFP and subsequent inoculation of GFP-expressing **tumor** cells (B02/GFP.2) in the mouse tail vein, B02/GFP.2 cells displayed a unique predilection for dissemination to bone. Externally fluorescence imaging of live animals allowed the detection of fluorescent bone metastases approx. 1 wk before the occurrence of radiol. distinctive osteolytic lesions. The no., size, and intensity of fluorescent bone metastases increased progressively with time and was indicative of breast **cancer** cell progression within bone. Histol. examn. of fluorescent long bones from B02/GFP.2-bearing mice revealed the occurrence of profound bone destruction. Treatment of B02/GFP.2-bearing mice with the **bisphosphonate zoledronic** acid markedly inhibited

the progression of established osteolytic lesions and the expansion of breast **cancer** cells within bone. Overall, this new bone metastasis model of breast **cancer** combining both fluorescence imaging and radiog. should provide an invaluable tool to study the effectiveness of pharmaceutical agents that could suppress **cancer** colonization in bone.

IT Antitumor agents
(bone; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Disease models
Human
(early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Imaging
(fluorescent; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Proteins
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(green fluorescent; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Bone, **neoplasm**
(metastasis; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Mammary gland
(**neoplasm**; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT Bone, disease
(osteolysis; early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

IT **118072-93-8, Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(early detection of bone metastases in murine model using fluorescent human breast **cancer** cells and application to use of **bisphosphonate zoledronic** acid in treatment of osteolytic lesions)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:582508 CAPLUS
DOCUMENT NUMBER: 135:339158
TITLE: Safety and efficacy of **bisphosphonates** beyond 24 months in **cancer** patients
AUTHOR(S): Ali, S. M.; Esteva, F. J.; Hortobagyi, G.; Harvey, H.; Seaman, J.; Knight, R.; Costa, L.; Lipton, A.
CORPORATE SOURCE: M.S. Hershey Medical Center, Hershey, PA, USA
SOURCE: Journal of Clinical Oncology (2001), 19(14), 3434-3437

CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bisphosphonate** therapy has decreased the risk of skeletal complications assocd. with osteolytic bone lesions in patients with breast **cancer** and multiple myeloma. The large prospective studies have used 21 to 24 mo of treatment. We studied the safety and efficacy of **bisphosphonates** in a subset of patients who received therapy for more than 24 mo. Patients who received **bisphosphonates** (pamidronate or **zoledronic** acid) were identified. Data on skeletal events and lab. parameters were gathered by chart review. We studied 22 patients who received i.v. pamidronate or **zoledronic** acid for a duration of 3.6 yr (range, 2.2 to 6.0 yr). Prolonged therapy was well tolerated. No significant calcium, phosphorus, electrolyte, or WBC count abnormalities were encountered. There was a clin. insignificant decrease in Hb and platelet count and an increase in creatinine in these patients. The fracture rate beyond 2 yr was no greater than during the first 2 yr of treatment. There were no stress fractures of long bones with prolonged therapy. Prolonged treatment with the potent **bisphosphonates** pamidronate and **zoledronic** acid seems to be well tolerated and should be studied in prospective, randomized studies to document prolonged skeletal efficacy.

IT Multiple myeloma
Skeleton
(efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT Mammary gland
(**neoplasm**; efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate**; efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

IT 57248-88-1, Aredia **118072-93-8**, Zometa
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of **bisphosphonates** beyond 24 mo in **cancer** humans)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:418592 CAPLUS
DOCUMENT NUMBER: 136:160948
TITLE: The **bisphosphonate, zoledronic** acid, induces apoptosis of breast **cancer** cells: Evidence for synergy with paclitaxel
AUTHOR(S): Jagdev, S. P.; Coleman, R. E.; Shipman, C. M.; Rostami-H, A.; Croucher, P. I.
CORPORATE SOURCE: YCR Department of Clinical Oncology, Weston Park Hospital, Sheffield, UK
SOURCE: British Journal of Cancer (2001), 84(8), 1126-1134
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bisphosphonates** are well established in the management of breast-**cancer**-induced bone disease. Recent studies have

suggested that these compds. are effective in preventing the development of bone metastases. However, it is unclear whether this reflects an indirect effect via an inhibition of bone resorption or a direct antitumor effect. The breast **cancer** cell lines, MCF-7 and MDA-MB-231 cells were treated with increasing concns. of the **bisphosphonate**, **zoledronic** acid, for varying time periods, in the presence or absence of paclitaxel. The effects of **zoledronic** acid were detd. by assessing cell no. and rate of apoptosis by evaluating changes in nuclear morphol. and using a fluorescence nick translation assay. **Zoledronic** acid caused a dose- and time-dependent decrease in cell no. ($P < 0.001$) and a concomitant increase in **tumor** cell apoptosis ($P < 0.005$). Short-term exposure to **zoledronic** acid was sufficient to cause a significant redn. in cell no. and increase in apoptosis ($P < 0.05$). These effects could be prevented by incubation with geranyl geraniol, suggesting that **zoledronic** acid-induced apoptosis is mediated by inhibiting the mevalonate pathway. Treatment with **zoledronic** acid and clin. achievable concns. of paclitaxel resulted in a 4-5-fold increase in **tumor** cell apoptosis ($P < 0.02$). Isobologram anal. revealed synergistic effects on **tumor** cell no. and apoptosis when **zoledronic** acid and paclitaxel were combined. Short-term treatment with **zoledronic** acid, which closely resembles the clin. setting, has a clear antitumor effect on breast **cancer** cells. Importantly, the commonly used anti-neoplastic agent, paclitaxel, potentiates the antitumor effects of **zoledronic** acid. These data suggest that, in addn. to inhibiting bone resorption, **zoledronic** acid has a direct antitumor activity on breast **cancer** cells in vitro.

IT Antitumor agents
(mammary gland; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Mammary gland
(**neoplasm**, inhibitors; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Drug interactions
(synergistic; **zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT Apoptosis
(**zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

IT 33069-62-4, Paclitaxel **118072-93-8**, **Zoledronic** acid
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid induces apoptosis of breast **cancer** cells and evidence for synergy with paclitaxel)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:307374 CAPLUS
DOCUMENT NUMBER: 135:220794
TITLE: A phase I dose-ranging trial of monthly infusions of **zoledronic** acid for the treatment of osteolytic bone metastases
AUTHOR(S): Berenson, James R.; Vescio, Robert A.; Rosen, Lee S.; VonTeichert, Joseph M.; Woo, Margie; Swift, Regina; Savage, Allison; Givant, Elise; Hupkes, Mieke; Harvey, Harold; Lipton, Allan
CORPORATE SOURCE: Division of Hematology and Oncology, Cedars-Sinai Medical Center, Los Angeles, CA, 90048, USA
SOURCE: Clinical Cancer Research (2001), 7(3), 478-485
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Bisphosphonates** are potent inhibitors of bone resorption and provide a therapeutic benefit for patients with bone metastases. **Zoledronic** acid is a highly potent, nitrogen-contg. **bisphosphonate**. In the present trial, we assessed the safety and tolerability of increasing doses of **zoledronic** acid and its effects on urinary markers of bone resorption in **cancer** patients with bone metastases. Fifty-nine **cancer** patients with bone metastases were enrolled sequentially into one of 8 treatment groups in the core protocol. Each patient received a 5-min i.v. infusion of 0.1, 0.2, 0.4, 0.8, 1.5, 2, 4, or 8 mg **zoledronic** acid monthly for 3 mo. Patients were monitored for clin. findings, adverse events, electrocardiograms, markers of bone resorption, as well as routine hematol., blood chemistries, and urinalysis. Thirty patients who demonstrated a radiog. response to treatment or stable disease in the core protocol were enrolled in a humanitarian extension protocol and continued to receive monthly infusions. **Zoledronic** acid was well tolerated at all dose levels. Adverse events reported by >10% of patients included skeletal pain, nausea, fatigue, upper respiratory tract infection, constipation, headache, diarrhea, and fever. Three patients in the core protocol and one patient in the extension protocol experienced grade 3 skeletal pain, "flulike" symptoms, or hypophosphatemia, which were possibly related to treatment; all recovered completely. Adverse events were reported with similar frequency across all of the dosage groups. **Zoledronic** acid resulted in sustained, dose-dependent decreases in urinary markers of bone resorption. **Zoledronic** acid was safe and well tolerated and demonstrated potent inhibition of bone resorption.
IT Bone, **neoplasm**
(metastasis; increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
IT Bone
(resorption, inhibitors; increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
IT **118072-93-8, zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(increasing doses of **zoledronic** acid in treatment of osteolytic bone metastases in humans)
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:278266 CAPLUS
DOCUMENT NUMBER: 135:189951
TITLE: **Zoledronic** acid reduces skeletal-related events in patients with osteolytic metastases: A double-blind, randomized dose-response study
AUTHOR(S): Berenson, James R.; Rosen, Lee S.; Howell, Anthony; Porter, Lester; Coleman, Robert E.; Morley, Walter; Dreicer, Robert; Kuross, Steven A.; Lipton, Allan; Seaman, John J.
CORPORATE SOURCE: Cedars-Sinai Medical Center, Los Angeles, CA, USA
SOURCE: Cancer (New York, NY, United States) (2001), 91(7), 1191-1200
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study evaluated the dose-response relation for **zoledronic**

acid, a new generation high-potency **bisphosphonate**, given as a 5-min infusion in patients with malignant osteolytic disease. Two-hundred eighty patients with osteolytic lesions due to metastatic breast carcinoma or multiple myeloma were randomized to double-blind treatment with 0.4, 2.0, or 4.0 mg of **zoledronic** acid or 90 mg pamidronate. The primary efficacy endpoint was the proportion of patients receiving radiation to bone. Other skeletal-related events, bone mineral d. (BMD), bone markers, Eastern Cooperative Oncol. Group performance status, pain and analgesic scores, and safety also were evaluated. **Zoledronic** acid at doses of 2.0 and 4.0 mg and pamidronate at a dose of 90 mg each significantly reduced the need for radiation therapy to bone ($P < 0.05$) in contrast with 0.4 mg **zoledronic** acid, which did not. Skeletal-related events of any kind, pathol. fractures, and hypercalcemia also occurred less frequently in patients treated with 2.0 or 4.0 mg **zoledronic** acid or pamidronate than with 0.4 mg **zoledronic** acid. Increases in lumbar spine BMD (6.2-9.6%) and decreases in the bone resorption marker N-telopeptide (range, -37.1 to -60.8%) were obsd. for all treatment groups. Skeletal pain, fatigue, nausea, vomiting, and headache were the most commonly reported adverse events. Adverse events were similar in nature and frequency with **zoledronic** acid and pamidronate. A 5-min infusion of 2.0-4.0 mg **zoledronic** acid was at least as effective as a 2-h 90-mg pamidronate infusion in treatment of osteolytic metastases. A 0.4-mg dose of **zoledronic** acid was significantly less effective. Both **zoledronic** acid and pamidronate were well tolerated.

IT Bone, **neoplasm**
(metastasis; **zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**zoledronic** acid reduces skeletal-related events in humans with osteolytic metastases)

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:82572 CAPLUS
DOCUMENT NUMBER: 135:132357
TITLE: A phase I, open label, dose ranging trial of intravenous bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease
AUTHOR(S): Berenson, James R.; Vescio, Robert; Henick, Kathryn; Nishikubo, Carol; Retting, Matthew; Swift, Regina A.; Conde, Francisco; Von Teichert, Joseph M.
CORPORATE SOURCE: Department of Medicine, Cedars Sinai Medical Center, Los Angeles, CA, 90048, USA
SOURCE: Cancer (New York) (2001), 91(1), 144-154
CODEN: CANCAR; ISSN: 0008-543X
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bone metastases typically are assocd. with osteolytic bone destruction, resulting in bone pain, pathol. fractures, spinal cord compression, and hypercalcemia. **Bisphosphonates** are potent inhibitors of normal and pathol. bone resorption and represent a significant therapeutic improvement in the management of patients with lytic bone metastases. **Zoledronic** acid is a new generation, highly potent, nitrogen-contg. **bisphosphonate** that to the authors knowledge is the most potent inhibitor of bone resorption currently in clin. trials.

The objectives of the current study were to assess the safety and tolerability of increasing doses of **zoledronic** acid and to det. its activity with respect to reducing biochem. markers of bone resorption in **cancer** patients with bone metastases. Forty-four **cancer** patients with bone metastases or primary bone lesions were enrolled sequentially into 1 of 5 fixed ascending-dose treatment groups. Each patient received a single i.v. bolus injection of 1, 2, 4, 8, or 16 mg of **zoledronic** acid over 30-60 s. Patients were monitored for 8 wk for the evaluation of clin. findings, adverse events, vital signs, electrocardiograms, markers of bone resorption, and urinary N-acetyl-.beta.-D-glucosaminidase. **Zoledronic** acid was safe and well tolerated at all dose levels tested. Commonly reported adverse events included bone pain, fever, anorexia, constipation, and nausea, which were experienced by a similar proportion of patients in each treatment group. Seven patients reported serious adverse events, none of which appeared to be related to the study drug. **Zoledronic** acid effectively suppressed biochem. markers of bone resorption, including the highly specific markers N-telopeptide and deoxypyridinoline, for up to 8 wk in the 2-16-mg dose groups and for a shorter duration in the 1-mg group. In the current study, **zoledronic** acid was safe and well tolerated and demonstrated potent inhibition of bone resorption. The authors believe it may improve the treatment of metastatic bone disease.

IT Peptides, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(N-Telopeptide; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT Bone, **neoplasm**
(metastasis; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT Bone
(resorption, inhibitors; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT **118072-93-8**, **Zoledronic** acid
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT 83462-55-9, Deoxypyridinoline
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

IT 9012-33-3, N-Acetyl-.beta.-D-glucosaminidase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(urinary; i.v. bolus **zoledronic** acid, a novel **bisphosphonate**, in **cancer** patients with metastatic bone disease)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:51861 CAPLUS
DOCUMENT NUMBER: 135:131487
TITLE: Myeloma - the therapeutic challenge
AUTHOR(S): Berenson, James R.
CORPORATE SOURCE: Cedars-Sinai Medical Center, UCLA School of Medicine,

SOURCE: Los Angeles, CA, USA
Medizinische Klinik (Muenchen) (2000), 95(Suppl. 2), 19-21
CODEN: MEKLA7; ISSN: 0723-5003
PUBLISHER: Urban & Vogel Medien und Medizin Verlagsgesellschaft mbH
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 20 refs. Bone loss, the major clin. manifestation of multiple myeloma, often leads to pathol. fractures, spinal cord compression, hypercalcemia and bone pain. Analgesics, surgery and radiotherapy may effectively palliate patients with complications from myeloma bone disease, but cannot slow the progressive bone loss. Chemotherapy may reduce **tumor** burden but has little impact on the underlying bone disease. A dramatic change was the demonstration that i.v. pamidronate could reduce skeletal complications. Importantly, because **bisphosphonates** lack significant bone marrow suppressive effects they can be administered to other cytotoxic therapy. Lab. studies show the improved potency of the 3rd-generation **bisphosphonate** **zoledronic** acid in its anti-bone resorptive as well as anti-myeloma effects. Phase-I and -II studies evaluating **zoledronic** acid in myeloma patients show marked and sustained inhibition of bone resorption markers. The randomized studies evaluating **zoledronic** acid have demonstrated its superiority to pamidronate in overcoming **tumor**-induced hypercalcemia. Results of ongoing phase-III studies will det. its relative safety and efficacy compared to pamidronate.

IT Antitumor agents
(myeloma; therapeutic challenges in treating multiple Myeloma)

IT Bone
(resorption; therapeutic challenges in treating multiple Myeloma)

IT Multiple myeloma
(therapeutic challenges in treating multiple Myeloma)

IT **118072-93-8**, **Zoledronic** acid
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic challenges in treating multiple Myeloma)

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:841963 CAPLUS
DOCUMENT NUMBER: 134:524
TITLE: Methods and pharmaceutical compositions using **bisphosphonates** for the treatment of **angiogenesis**
INVENTOR(S): Okuno, Tetsuji; Green, Jonathan; Wood, Jeanette Marjorie
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071104	A2	20001130	WO 2000-EP4562	20000519
WO 2000071104	A3	20010719		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1178810	A2	20020213	EP 2000-936760	20000519
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010808	A	20020827	BR 2000-10808	20000519
JP 2003500352	T2	20030107	JP 2000-619411	20000519
NO 2001005638	A	20020115	NO 2001-5638	20011119
US 2002142996	A1	20021003	US 2001-989577	20011120

PRIORITY APPLN. INFO.:

GB 1999-11926	A	19990521
GB 1999-25131	A	19991022
WO 2000-EP4562	W	20000519

AB A method is provided for the treatment of **angiogenesis** in a patient in need of such treatment, e.g. a **tumor** patient or a patient suffering from an **inflammatory** disease, which comprises administering, preferably via an intra-arterial route, an effective amt. of a **bisphosphonate**, e.g. pamidronic acid or **zoledronic** acid or salts or hydrates thereof, to the patient.

IT Animal cell line
(HUVEC; **bisphosphonate** for **angiogenesis** treatment)

IT **Angiogenesis** inhibitors
Anti-**inflammatory** agents
Anti-ischemic agents
Antiarthritics
Antirheumatic agents
Antitumor agents
Cell migration
(**bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(capsules; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(carcinoma, A431 cell; **bisphosphonate** for **angiogenesis** treatment)

IT Blood vessel
(endothelium; **bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(freeze-dried; **bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(infusions, i.v.; **bisphosphonate** for **angiogenesis** treatment)

IT Heart, disease
(**ischemia**; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(lung, metastasis, from breast; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(mammary gland, metastasis, to lung; **bisphosphonate** for **angiogenesis** treatment)

IT Lung, **neoplasm**
(metastasis, inhibitors, from breast; **bisphosphonate** for **angiogenesis** treatment)

IT Mammary gland
(metastasis, inhibitors, to lung; **bisphosphonate** for **angiogenesis** treatment)

IT Antitumor agents
(metastasis; **bisphosphonate** for **angiogenesis** treatment)

IT Proliferation inhibition
(proliferation inhibitors; **bisphosphonate** for **angiogenesis** treatment)

IT Drug delivery systems
(transdermal; **bisphosphonate** for **angiogenesis** treatment)

IT 132508-02-2, U 81581
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(U 81581; **bisphosphonate** for **angiogenesis** treatment)

IT 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**bisphosphonate** for **angiogenesis** treatment)

IT **2809-21-4**, Etidronic acid **10596-23-3**, Clodronic acid
13598-36-2D, Phosphonic acid, **bisphosphonates** **40391-99-9**, Pamidronic acid 57248-88-1, Disodium pamidronate **63132-39-8**
66376-36-1, Alendronic acid **79778-41-9**
89987-06-4, Tiludronic acid **105462-24-6**, Risedronic acid
105462-24-6D, Risedronic acid, N-Me pyridinium salts 112855-84-2, FR 78844 **114084-78-5**, Ibandronic acid **118072-93-8**, **Zoledronic** acid 118072-93-8D, mixed sodium salts 125946-91-0
125946-92-1, EB 1053 132423-94-0 138844-81-2, BM 21.0955
180064-38-4, YM 529 183490-29-1, **NE 10446**
197313-76-1, **NE 10244**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**bisphosphonate** for **angiogenesis** treatment)

=>

L15 ANSWER 4 OF 14 USPATFULL

ACCESSION NUMBER:	2002:329505 USPATFULL
TITLE:	Method of treating restenosis using **bisphosphonate** nanoparticles
INVENTOR(S):	Golomb, Gershon, Efrat, ISRAEL Danenberg, Haim, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002187184	A1	20021212
APPLICATION INFO.:	US 2002-126248	A1	20020419 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-743705, filed on 22 Mar 2001, PENDING A 371 of International Ser. No. WO 1999-IL387, filed on 14 Jul 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-125336	19980714

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	MORGAN & FINNEGAN, L.L.P., 345 Park Avenue, New York, NY, 10154-0053
NUMBER OF CLAIMS:	34
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	10 Drawing Page(s)
LINE COUNT:	1265

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating or preventing restenosis by administering to an individual an effective amount of an active ingredient comprising a **bisphosphonate** particle or a **bisphosphonate** particulate. The **bisphosphonate** may be encapsulated, embedded or adsorbed within the particle, dispersed uniformly in the polymer matrix, adsorbed on the particle surface, or in combination of any of these forms. The particles include liposomes or inert polymeric particles, such as microcapsules, nanocapsules, nanoparticles, nanospheres, or microparticles. The particulates include any suspended or dispersed form of the **bisphosphonate** which is not encapsulated, entrapped, or adsorbed within a polymeric particle. The particulates include suspended or dispersed colloids, aggregates, flocculates, insoluble salts and insoluble complexes of the active ingredient. The active ingredient effects restenosis by inhibiting the growth and proliferation of the cell types involved in the restenotic cascade, such as macrophages/monocytes, fibroblasts and smooth-muscle cells.

ACCESSION NUMBER: 2003:17932 USPATFULL
TITLE: Method of inhibiting restenosis using **bisphosphonates**
INVENTOR(S): Golomb, Gershon, Efrat, ISRAEL
Danenberg, Haim, Brookline, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003013686	A1	20030116
APPLICATION INFO.:	US 2002-160207	A1	20020530 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2002-126248, filed on 19 Apr 2002, PENDING Continuation-in-part of Ser. No. US 2001-743705, filed on 22 Mar 2001, PENDING A 371 of International Ser. No. WO 1999-IL387, filed on 14 Jul 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-125336	19980714

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MORGAN & FINNEGAN, L.L.P., 345 Park Avenue, New York, NY, 10154-0053
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1039

AB A method of inhibiting the activity or production of cytokines or growth factors associated with vascular restenosis, by administering to an individual an effective amount of an active ingredient comprising a **bisphosphonate** particle or a **bisphosphonate** particulate. The **bisphosphonate** may be encapsulated, embedded or adsorbed within the particle, dispersed uniformly in the polymer matrix, adsorbed on the particle surface, or in combination of any of these forms. The particles include liposomes or inert polymeric particles, such as microcapsules, nanocapsules, nanoparticles, nanospheres, or microparticles. The particulates include any suspended or dispersed form of the **bisphosphonate** which is not encapsulated, entrapped, or adsorbed within a polymeric particle. The particulates include suspended or dispersed colloids, aggregates, flocculates, insoluble salts and insoluble complexes of the active ingredient. The cytokines and growth factors include, but are not limited to interleukin 1-.beta., matrix metalloproteinase-2, and platelet-derived growth factor .beta. (PDGF.beta.).